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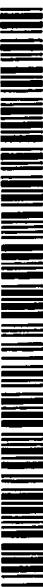
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(54) Title: METHOD FOR TREATING CHRONIC PAIN USING MEK INHIBITORS

(57) Abstract: The invention features a method for treating chronic pain using disclosed diarylamines.

## METHOD FOR TREATING CHRONIC PAIN USING MEK INHIBITORS

5

### BACKGROUND

The invention features a method for treating chronic pain using MEK inhibitors. Chronic pain includes neuropathic pain, and chronic inflammatory pain.

10

Abnormality anywhere in a nerve pathway disrupts nerve signals, which in turn are abnormally interpreted in the brain, causing neuropathic pain. Neuropathic pain may be, for example, a deep ache, a burning sensation, or hypersensitivity to touch. Diseases or conditions associated with neuropathic pain include, without limitation, diabetic neuropathy, causalgia, plexus avulsion, neuroma, vasculitis, crush injury, viral infections (e.g., herpes virus infection or HIV), constriction injury, tissue injury, nerve injury from the periphery to the central nervous system, limb amputation, hypothyroidism, uremia, chronic alcoholism, post-operative pain, arthritis, back pain, and vitamin deficiencies.

Infections such as herpes zoster (shingles) can cause nerve inflammation and produce postherpetic neuralgia, a chronic burning localized to the area of viral infection. Hyperalgesia is when an already noxious stimulus becomes more painful, and allodynia, when a previously non-noxious stimulus becomes painful (such as contact of clothing or a breeze). Reflex sympathetic dystrophy is accompanied by swelling and sweating or changes in local blood flow, tissue atrophy, or osteoporosis. Causalgia, including severe burning pain and swelling, sweating, and changes in blood flow, may follow an injury or disease of a major nerve such as the sciatic nerve. Some types of chronic low back pain can have a neuropathic component (e.g., sciatica, postpoliomyelitis and CPRM). Neuropathic pain may also be induced by cancer or chemotherapy.

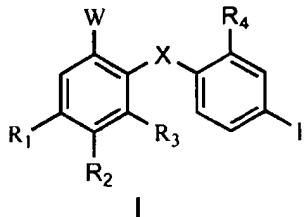
Neuropathic pain is currently treated with anticonvulsants such as carbamazepine and antidepressants such as amitryptaline. NSAIDS and opioids generally have little effect (*Fields et al 1994 Textbook of Pain p 991-996 (pub: Churchill Livingstone), James & Page 1994*

5 *J.Am.Pediatr.Med.Assoc, 8: 439-447, Galer, 1995 Neurology 45 S17-S25.*  
Neuropathic conditions that have been treated with gabapentin include:  
postherpetic neuralgia, postpoliomyelitis, CPRM, HIV-related neuropathy,  
trigeminal neuralgia, and reflex sympathetic dystrophy (RSD).  
The generally weak efficacy of antiinflammatory agents suggests that the  
10 mechanism for chronic pain is separate from hyperalgesia.

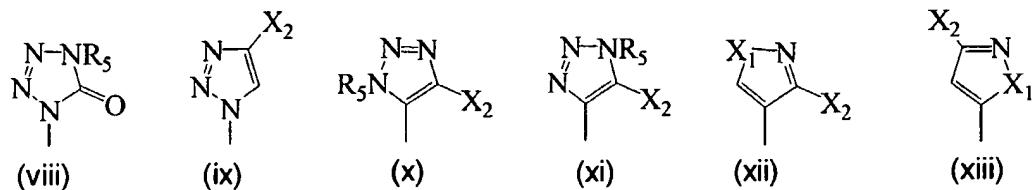
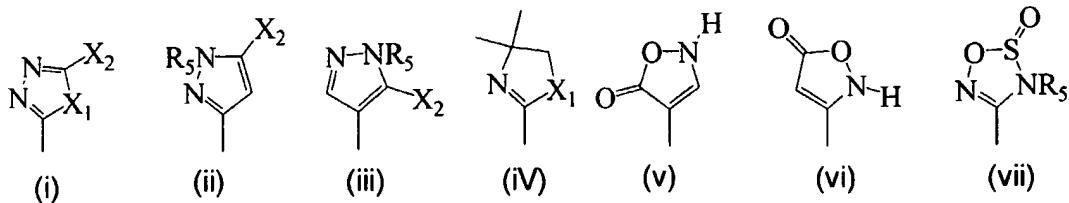
#### SUMMARY OF THE INVENTION

The invention features a method for treating chronic pain, which  
15 method includes the step of administering a composition including a MEK  
inhibitor to a patient in need of such treatment. Chronic pain includes  
neuropathic pain, idiopathic pain, and pain associated with vitamin  
deficiencies, uremia, hypothyroidism post-operative pain, arthritis, back pain,  
and chronic alcoholism. The invention also features compositions as  
20 disclosed, formulated for the treatment of chronic pain. Such a composition  
may include one or more MEK inhibitor compounds having a structure  
disclosed in patent application PCT/US99/30416, international filing date  
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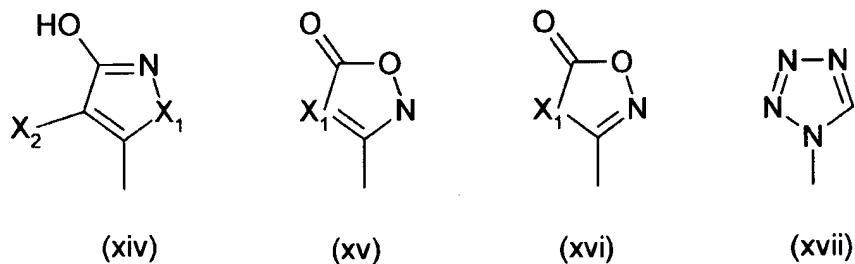
Examples of MEK inhibitors include a compound having the formula (I)  
25 below:



W is one of the following formulae (i) – (xiii):



5



10

X<sub>1</sub> is O, S, or NR<sub>E</sub>. X<sub>2</sub> is OH, SH, or NHR<sub>E</sub>. Each of R<sub>E</sub> and R<sub>F</sub> is H or C<sub>1-4</sub> alkyl; each of R<sub>1</sub> and R<sub>2</sub> is independently selected from H, F, NO<sub>2</sub>, Br and Cl; R<sub>1</sub> can also be SO<sub>2</sub>NR<sub>G</sub>R<sub>H</sub>, or R<sub>1</sub> and R<sub>2</sub> together with the benzene ring to which they are attached constitute an indole, isoindole, benzofuran, benzothiophene, indazole, benzimidazole, or benzthioazole. R<sub>3</sub> is selected from H and F; each of R<sub>G</sub>, R<sub>H</sub>, and R<sub>4</sub> is independently selected from H, Cl and CH<sub>3</sub>. R<sub>5</sub> is H or C<sub>1-4</sub> alkyl. Each hydrocarbon radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, hydroxyl, amino, (amino)sulfonyl, and NO<sub>2</sub>. Each heterocyclic radical

above is optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, phenyl, hydroxyl, amino, (amino)sulfonyl, and NO<sub>2</sub>, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 2 substituents independently selected from halo, C<sub>1-2</sub> alkyl, hydroxyl, amino, and NO<sub>2</sub>. The invention also features a pharmaceutically acceptable salt or C<sub>1-8</sub> ester of a disclosed compound. For example, the disclosed alcohol compounds may form esters having the structure obtained by replacing the H of a hydroxyl group with a -C(=O)C<sub>1-7</sub> acyl group.

Preferred embodiments of the invention include methods of using one or more of the following compounds:

(a) said MEK inhibitor has a structure selected from: 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid; 5-[3,4difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; (2,3-difluoro-6-[1,3,4]oxadiazol-2-yl-phenyl)(-4-iodo-2-methyl-phenyl)-amine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-ylamine; and 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; and

(b) said MEK inhibitor has the structure selected from: 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid.

Other aspects of the invention are provided in the description, examples and claims below.

#### BRIEF DESCRIPTION OF THE FIGURES

30 FIG. 1 is a bar graph representing the paw withdrawal threshold (PWT) in grams as a function of time in days. The empty, cross-hatched, and single-

hatched bars are vehicle, PD 198306, and pregabalin, respectively. The arrows indicate time of drug administration (30 mg/kg, p.o.).

5 FIG 2. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Baseline (BL) measurements were taken before treatment. Animals received a single p.o. administration of PD 198306 (3-30mg/kg), or pregabalin (30mg/kg) and withdrawal thresholds were re-assessed 1h after treatment. Treatments were repeated twice a day for two days. Results are expressed 10 median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*P<0.05, \*\*P<0.01, \*\*\*P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=7-8).

15 FIG. 3. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Baseline (BL) measurements were taken before treatment. Animals received a single p.o. administration of PD 198306 (3-30mg/kg), or pregabalin (30mg/kg) and withdrawal thresholds were re-assessed 1h after treatment. Treatments were repeated twice a day for two days. Results are expressed 20 median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*\*P<0.01 significantly different from vehicle treated animals (Mann-Whitney t test; n=6).

25 FIG. 4. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Baseline (BL) measurements were taken before treatment. Animals received a single i.t. administration of PD 198306 (1-30 $\mu$ g/10 $\mu$ l), or pregabalin (100 $\mu$ g/10 $\mu$ l) and withdrawal thresholds were re-assessed at 30min, 1h and 2h after treatment. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*P<0.05, \*\*\*P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=7-9).

30

FIG. 5. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days.

Baseline (BL) measurements were taken before treatment. Animals received a single i.t. administration of PD 198306 (1-30 $\mu$ g/10 $\mu$ l), or pregabalin (100 $\mu$ g/10 $\mu$ l) and withdrawal thresholds were re-assessed at 30min, 1h and 2h after treatment. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles.

5 \*P<0.05, \*\*P<0.01, \*\*\*P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=6-8).

FIG. 6 is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days.

10 Animals received a single intraplanter (i.pl.) administration of PD 198306 (3mg/100 $\mu$ l), or an intrathecal injection of PD 198306 (30 $\mu$ g/10 $\mu$ l) and withdrawal thresholds were re-assessed 1h after treatment. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*\*P<0.01 significantly different from vehicle treated animals (Mann-Whitney t test; n=6-9).

15

FIG. 7. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days.

Animals received a single intraplanter (i.pl.) administration of PD 198306 (3mg/100 $\mu$ l), or an intrathecal injection of PD 198306 (30 $\mu$ g/10 $\mu$ l) and withdrawal thresholds were re-assessed 1h after treatment. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*\*P<0.01 significantly different from vehicle treated animals (Mann-Whitney t test; n=6).

25

FIG. 8 is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments. Baseline (BL) measurements were taken before treatment. Animals received a single i.t. administration of PD219622, PD297447, PD 184352, or PD 254552 (30 $\mu$ g/10 $\mu$ l), or pregabalin (100 $\mu$ g/10 $\mu$ l) and withdrawal thresholds were re-assessed at 30min, 1h and 2h after treatment. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles.

30 \*P<0.05, \*\*P<0.01, \*\*\*P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=7-8).

## DETAILED DESCRIPTION

The compounds disclosed herein are pharmaceutically active, for example, they inhibit MEK. MEK enzymes are dual specificity kinases

5 involved in, for example, immunomodulation, inflammation, and proliferative diseases such as cancer and restenosis.

Proliferative diseases are caused by a defect in the intracellular signaling system, or the signal transduction mechanism of certain proteins.

Defects include a change either in the intrinsic activity or in the cellular

10 concentration of one or more signaling proteins in the signaling cascade. The cell may produce a growth factor that binds to its own receptors, resulting in an autocrine loop, which continually stimulates proliferation. Mutations or overexpression of intracellular signaling proteins can lead to spurious mitogenic signals within the cell. Some of the most common mutations occur

15 in genes encoding the protein known as Ras, a G-protein that is activated when bound to GTP, and inactivated when bound to GDP. The above-mentioned growth factor receptors, and many other mitogenic receptors, when activated, lead to Ras being converted from the GDP-bound state to the GTP-bound state. This signal is an absolute prerequisite for proliferation in most

20 cell types. Defects in this signaling system, especially in the deactivation of the Ras-GTP complex, are common in cancers, and lead to the signaling cascade below Ras being chronically activated.

Activated Ras leads in turn to the activation of a cascade of serine/threonine kinases. One of the groups of kinases known to require an active Ras-GTP for its own activation is the Raf family. These in turn activate MEK (e.g., MEK<sub>1</sub> and MEK<sub>2</sub>) which then activates MAP kinase, ERK (ERK<sub>1</sub> and ERK<sub>2</sub>). Activation of MAP kinase by mitogens appears to be essential for proliferation; constitutive activation of this kinase is sufficient to induce cellular transformation. Blockade of downstream Ras signaling, for example by use of a dominant negative Raf-1 protein, can completely inhibit mitogenesis, whether induced from cell surface receptors or from oncogenic Ras mutants. Although Ras is not itself a protein kinase, it participates in the activation of

Raf and other kinases, most likely through a phosphorylation mechanism. Once activated, Raf and other kinases phosphorylate MEK on two closely adjacent serine residues, S218 and S222 in the case of MEK-1, which are the prerequisite for activation of MEK as a kinase. MEK in turn phosphorylates

5 MAP kinase on both a tyrosine, Y185, and a threonine residue, T183, separated by a single amino acid.

This double phosphorylation activates MAP kinase at least 100-fold.

Activated MAP kinase can then catalyze the phosphorylation of a large number of proteins, including several transcription factors and other kinases.

10 Many of these MAP kinase phosphorylations are mitogenically activating for the target protein, such as a kinase, a transcription factor, or another cellular protein. In addition to Raf-1 and MEKK, other kinases activate MEK, and MEK itself appears to be a signal integrating kinase. Current understanding is that MEK is highly specific for the phosphorylation of MAP kinase. In fact, 15 no substrate for MEK other than the MAP kinase, ERK, has been demonstrated to date and MEK does not phosphorylate peptides based on the MAP kinase phosphorylation sequence, or even phosphorylate denatured MAP kinase. MEK also appears to associate strongly with MAP kinase prior to phosphorylating it, suggesting that phosphorylation of MAP kinase by MEK 20 may require a prior strong interaction between the two proteins. Both this requirement and the unusual specificity of MEK are suggestive that it may have enough difference in its mechanism of action to other protein kinases that selective inhibitors of MEK, possibly operating through allosteric mechanisms rather than through the usual blockade of the ATP binding site, 25 may be found.

The effect of the MEK inhibitor PD 198306 has been investigated in two animal models of neuropathic pain by assessing static allodynia with von Frey hairs.

Oral administration of PD 198306 (3-30mg/kg) had no effect in the model 30 of chronic constriction injury of the sciatic nerve (CCI). However, after repeated administration (3 doses over two days) it had a transient effect in the diabetic neuropathy model (streptozocin). This may be due to disorders of the blood-

brain barrier induced by the diabetic condition in these animals, thus allowing central action of the compound. Intrathecal administration of PD 198306 (1-30 $\mu$ g) dose-dependently blocked static allodynia in both the streptozocin and the CCI models of neuropathic pain, with minimum effective doses (MED) of 3 and 5 10 $\mu$ g respectively. The highest dose used (30 $\mu$ g) totally blocked the maintenance of static allodynia, for up to 1h. Intraplantar administration of PD 198306 (3mg/100 $\mu$ l) at a dose 100-fold higher than the dose shown to be effective intrathecally (30 $\mu$ g/10 $\mu$ l) had no effect on static allodynia in either of the neuropathic pain models. This finding confirms the lack of effect seen after 10 systemic administration and suggests a central site of action for the compound.

From this study we can suggest the use of MEK inhibitors as potential new therapeutic tools for chronic pain. The study of potential side-effects, especially related to memory, of future brain-penetrant MEK inhibitors will indicate the therapeutic window for this novel class of compounds in the 15 treatment of pain.

### A. Terms

Certain terms are defined below and by their usage throughout this disclosure.

Alkyl groups include aliphatic (i.e., hydrocarbyl or hydrocarbon radical) structures containing hydrogen and carbon atoms with a free valence. Alkyl groups are understood to include straight chain and branched structures. Examples include methyl, ethyl, propyl, isopropyl, butyl, n-butyl, isobutyl, t-butyl, pentyl, isopentyl, 2,3-dimethylpropyl, hexyl, 2,3-dimethylhexyl, 1,1-dimethylpentyl, heptyl, and octyl. Cycloalkyl groups include cyclopropyl, 10 cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

Alkyl groups can be substituted with 1, 2, 3 or more substituents which are independently selected from halo (fluoro, chloro, bromo, or iodo), hydroxy, amino, alkoxy, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, arylalkyloxy, heterocyclic radical, and (heterocyclic radical)oxy. Specific examples include 15 fluoromethyl, hydroxyethyl, 2,3-dihydroxyethyl, (2- or 3-furanyl)methyl, cyclopropylmethyl, benzyloxyethyl, (3-pyridinyl)methyl, (2- or 3-furanyl)methyl, (2-thienyl)ethyl, hydroxypropyl, aminocyclohexyl, 2-dimethylaminobutyl, methoxymethyl, N-pyridinylethyl, diethylaminoethyl, and cyclobutylmethyl.

Alkenyl groups are analogous to alkyl groups, but have at least one 20 double bond (two adjacent  $sp^2$  carbon atoms). Depending on the placement of a double bond and substituents, if any, the geometry of the double bond may be *entgegen* (E), or *zusammen* (Z), *cis*, or *trans*. Similarly, alkynyl groups have at least one triple bond (two adjacent  $sp$  carbon atoms).

Unsaturated alkenyl or alkynyl groups may have one or more double or triple 25 bonds, respectively, or a mixture thereof; like alkyl groups, unsaturated groups may be straight chain or branched, and they may be substituted as described both above for alkyl groups and throughout the disclosure by example. Examples of alkenyls, alkynyls, and substituted forms include *cis*-2-but enyl, trans-2-but enyl, 3-but enyl, 3-phenyl-2-propynyl, 3-(2'-fluorophenyl)-2-propynyl, 30 3-methyl(5-phenyl)-4-pentynyl, 2-hydroxy-2-propynyl, 2-methyl-2-propynyl, 2-propenyl, 4-hydroxy-3-but enyl, 3-(3-fluorophenyl)-2-propynyl, and 2-methyl-2-

propenyl. In formula (I), alkenyls and alkynyls can be C<sub>2-4</sub> or C<sub>2-8</sub>, for example, and are preferably C<sub>3-4</sub> or C<sub>3-8</sub>.

More general forms of substituted hydrocarbon radicals include hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, hydroxycycloalkyl, hydroxyaryl, 5 and corresponding forms for the prefixes amino-, halo- (e.g., fluoro-, chloro-, or bromo-), nitro-, alkyl-, phenyl-, cycloalkyl- and so on, or combinations of substituents. According to formula (I), therefore, substituted alkyls include hydroxyalkyl, aminoalkyl, nitroalkyl, haloalkyl, alkylalkyl (branched alkyls, such as methylpentyl), (cycloalkyl)alkyl, phenylalkyl, alkoxy, alkylaminoalkyl, 10 dialkylaminoalkyl, arylalkyl, aryloxyalkyl, arylalkyloxyalkyl, (heterocyclic radical)alkyl, and (heterocyclic radical)oxyalkyl. R<sub>1</sub> thus includes hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, hydroxycycloalkyl, hydroxyaryl, aminoalkyl, aminoalkenyl, aminoalkynyl, aminocycloalkyl, aminoaryl, alkylalkenyl, (alkylaryl)alkyl, (haloaryl)alkyl, (hydroxyaryl)alkynyl, and so forth. 15 Similarly, R<sub>A</sub> includes hydroxyalkyl and aminoaryl, and R<sub>B</sub> includes hydroxyalkyl, aminoalkyl, and hydroxyalkyl(heterocyclic radical)alkyl.

Heterocyclic radicals, which include but are not limited to heteroaryls, include: furyl, oxazolyl, isoxazolyl, thiophenyl, thiazolyl, pyrrolyl, imidazolyl, 20 1,3,4-triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, indolyl, and their nonaromatic counterparts. Further examples of heterocyclic radicals include piperidyl, quinolyl, isothiazolyl, piperidinyl, morpholinyl, piperazinyl, tetrahydrofuryl, tetrahydropyrrolyl, pyrrolidinyl, octahydroindolyl, octahydrobenzothiophenyl, and octahydrobenzofuranyl.

Selective MEK 1 or MEK 2 inhibitors are those compounds which 25 inhibit the MEK 1 or MEK 2 enzymes, respectively, without substantially inhibiting other enzymes such as MKK3, PKC, Cdk2A, phosphorylase kinase, EGF, and PDGF receptor kinases, and C-src. In general, a selective MEK 1 or MEK 2 inhibitor has an IC<sub>50</sub> for MEK 1 or MEK 2 that is at least one-fiftieth (1/50) that of its IC<sub>50</sub> for one of the above-named other enzymes. Preferably, 30 a selective inhibitor has an IC<sub>50</sub> that is at least 1/100, more preferably 1/500, and even more preferably 1/1000, 1/5000, or less than that of its IC<sub>50</sub> or one or more of the above-named enzymes.

## B. Compounds

One aspect of the invention features the disclosed compounds shown in formula (I) in the Summary section.

5 Embodiments of the invention include compounds wherein: (a)  $R_1$  is bromo or chloro; (b)  $R_2$  is fluoro; (c)  $R_3$  is H; (d) each of  $R_2$  and  $R_3$  is H; (e) each of  $R_2$  and  $R_3$  is fluoro; (f)  $R_1$  is bromo; (g) each of  $R_1$ ,  $R_2$  and  $R_3$  is fluoro; (h)  $R_2$  is nitro; (i)  $R_3$  is H; (j)  $R_4$  is chloro; (k)  $R_4$  is methyl; (l)  $R_5$  is H; (m)  $R_5$  is  $CH_3$ ; (n)  $X_1$  is O or S; (o)  $X_1$  is NH or  $NCH_3$ ; (p)  $X_2$  is OH, SH, or  $NH_2$ ; (q)  $X_2$  is OH; (r)  $X_2$  is  $NHR_E$ ; (s)  $R_4$  is H; (t)  $R_4$  is chloro or methyl; or 10 combinations thereof.

Preferably, where one of the substituents on a heterocyclic radical is an alkenyl or alkynyl group, the double or triple bond, respectively, is not adjacent the point of attachment when it is a heteroatom. For example, in such a situation, the substituent is preferably prop-2-ynyl, or but-2 or 3-enyl, and less preferably prop-1-ynyl or but-1-enyl.

phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol;

5 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; and 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ol.

10 Further examples include: 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine;

15 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazol-2-ylamine;

20 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ylamine;

25 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ylamine;

30 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-

thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; and 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazole-3-thiol.

Additional examples are: 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isoxazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1H-pyrazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-

phenylamino)-phenyl]-isothiazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isothiazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 1-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; and 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1-methyl-1H-pyrazol-3-ol.

The invention also features compounds such as: 5-[2-(2-amino-4-iodo-phenylamino)-4-fluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-3,4-difluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-3,4,5-trifluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-5-bromo-3,4-difluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-4-fluoro-5-nitro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 3-methyl-5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3H-[1,2,3]triazol-4-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 2-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-pyrazol-3-ol; 4-[5-

bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-2-methyl-2H-pyrazol-3-ol; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1,4-dihydro-tetrazol-5-one; 1-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; and 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1H-[1,2,3]triazol-4-ol.

15 Further examples of the invention include 3-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-2H-isoxazol-5-one; [5-fluoro-2-(2-oxo-2,3-dihydro-2I>4-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-[4-iodo-2-methyl-phenyl]-amine; [2,3-difluoro-6-(2-oxo-2,3-dihydro-2I>4-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-[4-iodo-2-methyl-phenyl]-amine; (4-iodo-2-methyl-phenyl)-[2,3,4-trifluoro-6-(2-oxo-2,3-dihydro-2I>4-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-amine;

20 [4-bromo-2,3-difluoro-6-(2-oxo-2,3-dihydro-2I>4-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-[4-iodo-2-methyl-phenyl]-amine; [5-fluoro-4-nitro-2-(2-oxo-2,3-dihydro-2I>4-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-[4-iodo-2-methyl-phenyl]-amine; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-

one; and 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-isoxazol-5-one.

Further compounds, where R<sub>1</sub> can also be SO<sub>2</sub>NR<sub>G</sub>R<sub>H</sub>, or R<sub>1</sub> and R<sub>2</sub> together with the benzene ring to which they are attached constitute an indole,

5 isoindole, benzofuran, benzothiophene, indazole, benzimidazole, or benzthioazole, include the following groups:

Group 1

10 (1) 2-Fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide  
(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-N-methyl-benzenesulfonamide  
(3) 2,3-Difluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzenesulfonamide  
15 (4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-N-methyl-N-(3-morpholin-4-yl-propyl)-benzenesulfonamide  
(5) 2-Fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide  
20 (6) N-(2-Dimethylamino-ethyl)-2-fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-phenylamino)-N-methyl-benzenesulfonamide

25 Group 2

(1) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide  
(2) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro- benzenesulfonamide  
30 (3) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

- (4) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide
- (5) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide
- 5 (6) 4-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-5-(4-iodo-phenylamino)-benzenesulfonamide

**Group 2b**

- 10 (1) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (2) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-N-methyl-N-(3-morpholin-4-yl-propyl)-benzenesulfonamide
- (3) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- 15 (4) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide
- (5) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzenesulfonamide
- 20 (6) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-N-(3-piperidin-1-yl-propyl)-benzenesulfonamide

**Group 3**

- 25 (1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-mercaptop-1,3,4-oxadiazol-2-yl)-benzenesulfonamide
- (2) 2-Fluoro-5-(4-iodo-phenylamino)-4-(5-mercaptop-1,3,4-oxadiazol-2-yl)-benzenesulfonamide
- (3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-mercaptop-1,3,4-oxadiazol-2-yl)-benzenesulfonamide
- 30 (4) 2-Fluoro-4-(4-iodo-phenylamino)-5-(5-mercaptop-1,3,4-oxadiazol-2-yl)-benzenesulfonamide

- (5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-mercaptop-1,3,4-oxadiazol-2-yl)-benzenesulfonamide
- (6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-mercaptop-1,3,4-oxadiazol-2-yl)-benzenesulfonamide

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## Group 4

- (1) 2-Fluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (2) 2-Fluoro-4-(5-hydroxy-1,3,4-thiadiazol-2-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide
- (3) 2,3-Difluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (4) 2-Fluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide
- 15 (5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-benzenesulfonamide
- (6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-benzenesulfonamide

20 Group 5

- (1) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (2) 4-(5-Amino-1,3,4-thiadiazol-2-yl)-5-(4-iodo-phenylamino)-2-mercaptop-benzenesulfonamide
- 25 (3) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (4) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide
- (5) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide
- 30 (6) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

## Group 6

(1) 2-Fluoro-5-(5-hydroxy-4H-1,2,4-triazol-3-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

5 (2) 2-Fluoro-4-(5-hydroxy-4H-1,2,4-triazol-3-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide

(3) 2,3-Difluoro-5-(5-hydroxy-4H-1,2,4-triazol-3-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-[4-(2-Dimethylamino-ethyl)-5-hydroxy-4H-1,2,4-triazol-3-yl]-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

10 (5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-4H-1,2,4-triazol-3-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-4-methyl-4H-1,2,4-triazol-3-yl)-benzenesulfonamide

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## Group 7

(1) 5-(5-Amino-4H-1,2,4-triazol-3-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

20 (2) 4-(5-Amino-4H-1,2,4-triazol-3-yl)-2-fluoro-5-(4-iodo-phenylamino)-benzenesulfonamide

(3) 5-(5-Amino-4-methyl-4H-1,2,4-triazol-3-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-[5-Amino-4-(3-dimethylamino-propyl)-4H-1,2,4-triazol-3-yl]-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

25 (5) 5-(5-Amino-4H-1,2,4-triazol-3-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide

(6) 5-(5-Amino-4-methyl-4H-1,2,4-triazol-3-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

30 Group 8

(1) 2-Fluoro-5-(3-hydroxy-isoxazol-5-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 2-Fluoro-4-(3-hydroxy-isoxazol-5-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide

(3) 2,3-Difluoro-5-(3-hydroxy-isoxazol-5-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

5 (4) 2-Fluoro-5-(3-hydroxy-isoxazol-5-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide

(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-hydroxy-isoxazol-5-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(3-hydroxy-isoxazol-5-yl)-benzenesulfonamide

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## Group 9

(1) 5-(3-Amino-isoxazol-5-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

15 (2) 4-(3-Amino-isoxazol-5-yl)-2-bromo-5-(4-iodo-phenylamino)-benzenesulfonamide

(3) 5-(3-Amino-isoxazol-5-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(3-Amino-isoxazol-5-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

20 (5) 5-(3-Amino-isoxazol-5-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide

(6) 5-(3-Amino-isoxazol-5-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

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## Group 10

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-mercaptop-isoxazol-5-yl)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(3-mercaptop-isoxazol-5-yl)-benzenesulfonamide

30 (3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-mercaptop-isoxazol-5-yl)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-mercaptop-isoxazol-5-yl)-benzenesulfonamide

(5) 2-Fluoro-4-(4-iodo-phenylamino)-5-(3-mercaptop-isoxazol-5-yl)-benzenesulfonamide

5 (6) 2-Bromo-5-(4-iodo-phenylamino)-4-(3-mercaptop-isoxazol-5-yl)-benzenesulfonamide

Group 11

10 (1) 2-Fluoro-5-(3-hydroxy-isoxazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(3-hydroxy-isoxazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-5-(3-hydroxy-isoxazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

15 (4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-hydroxy-isoxazol-4-yl)-benzenesulfonamide

(5) 2-Fluoro-5-(3-hydroxy-isoxazol-4-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 2-Bromo-4-(3-hydroxy-isoxazol-4-yl)-5-(4-iodo-phenylamino)-

20 benzenesulfonamide

Group 12

25 (1) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

(3) 5-(3-Amino-isoxazol-4-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-

30 benzenesulfonamide

(5) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 4-(3-Amino-isoxazol-4-yl)-2-chloro-5-(4-iodo-phenylamino)-  
benzenesulfonamide

Group 13

5 (1) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-  
benzenesulfonamide

(2) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-  
benzenesulfonamide

(3) 5-(3-Amino-isoxazol-4-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-  
10 benzenesulfonamide

(4) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-  
benzenesulfonamide"

(5) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-phenylamino)-  
benzenesulfonamide

15 (6) 4-(3-Amino-isoxazol-4-yl)-2-chloro-5-(4-iodo-phenylamino)-  
benzenesulfonamide

Group 14

20 (1) 5-(2-Amino-5H-pyrrol-3-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-  
benzenesulfonamide

(2) 5-(2-Amino-5H-pyrrol-3-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-  
benzenesulfonamide

(3) 5-(2-Amino-5H-pyrrol-3-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-  
benzenesulfonamide

25 (4) 5-(2-Amino-5H-pyrrol-3-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-  
benzenesulfonamide

(5) 5-(2-Amino-5H-pyrrol-3-yl)-2-fluoro-4-(4-iodo-phenylamino)-  
benzenesulfonamide

(6) 4-(2-Amino-5H-pyrrol-3-yl)-2-chloro-5-(4-iodo-phenylamino)-  
30 benzenesulfonamide

## Group 15

(1) 2-Fluoro-5-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-1H-pyrazol-4-yl)-benzenesulfonamide

5 (3) 2,3-Difluoro-5-(5-hydroxy-1H-pyrazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-1H-pyrazol-4-yl)-benzenesulfonamide

10 (5) 2-Fluoro-5-{5-hydroxy-1-[3-(4-methyl-piperazin-1-yl)-propyl]-1H-pyrazol-4-yl}-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 2-Fluoro-4-(5-hydroxy-1H-pyrazol-4-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide

## 15 Group 16

(1) 2-Fluoro-5-(5-hydroxy-3-methyl-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-benzenesulfonamide

20 (3) 2,3-Difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-benzenesulfonamide

(5) 2-Fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide

25 (6) 2-Fluoro-5-{5-hydroxy-3-[2-(2-methoxy-ethoxy)-ethyl]-3H-1,2,3-triazol-4-yl}-4-(4-iodo-phenylamino)-benzenesulfonamide

## Group 17

30 (1) 2-Fluoro-5-(5-hydroxy-3-methyl-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

5 (4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-benzenesulfonamide

(5) 2-Fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 2-Fluoro-5-{5-hydroxy-3-[2-(2-methoxy-ethoxy)-ethyl]-3H-1,2,3-triazol-4-yl}-4-(4-iodo-phenylamino)-benzenesulfonamide

10

## Group 18

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

15 (2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

20 (5) 2-Fluoro-4-(4-iodo-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(6) 2,6-Difluoro-3-(4-iodo-phenylamino)-4-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

25

## Group 19

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(4-methyl-5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(4-methyl-5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

30 (3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(5) 5-[4-(2-Dimethylamino-ethyl)-5-oxo-4,5-dihydro-tetrazol-1-yl]-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

5 (6) 2-Fluoro-5-(4-iodo-phenylamino)-4-(4-methyl-5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

Group 20

10 (1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

15 (4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(5) 2-Fluoro-4-(4-iodo-phenylamino)-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

20 (6) 2-Fluoro-5-(4-iodo-phenylamino)-4-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

Group 21

25 (1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(2) 2,6-Difluoro-3-(4-iodo-phenylamino)-4-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

30 (4) 2-Fluoro-4-(4-iodo-phenylamino)-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide  
(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-N-methyl-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

5

## Group 22

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide  
(2) 2,6-Difluoro-3-(4-iodo-phenylamino)-4-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide  
10 (3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide  
(4) 2-Fluoro-4-(4-iodo-phenylamino)-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide  
15 (5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide  
(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

20 Group 23

(1) 5-[6-(4-Iodo-2-methyl-phenylamino)-1H-benzimidazol-5-yl]-1,3,4-oxadiazol-2-ol  
(2) 5-[6-(4-Iodo-phenylamino)-benzofuran-5-yl]-1,3,4-oxadiazol-2-ol  
25 (3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzoxazol-5-yl]-1,3,4-oxadiazol-2-ol  
(4) 5-[5-(4-Iodo-phenylamino)-benzofuran-6-yl]-1,3,4-oxadiazol-2-ol  
(5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-1,3-dihydro-isobenzofuran-5-yl]-1,3,4-oxadiazol-2-ol  
30 (6) 5-[6-(2-Chloro-4-iodo-phenylamino)-1-methyl-1H-benzimidazol-5-yl]-1,3,4-oxadiazol-2-ol

## Group 24

(1) 5-[2-Amino-6-(4-iodo-2-methyl-phenylamino)-1H-benzimidazol-5-yl]-1,3,4-oxadiazol-2-ol

(2) 5-[6-(4-iodo-phenylamino)-benzo[b]thiophen-5-yl]-1,3,4-oxadiazol-2-ol

5 (3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol

(4) 5-[5-(4-iodo-phenylamino)-benzo[b]thiophen-6-yl]-1,3,4-oxadiazol-2-ol

(5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-1,3-dihydro-benzo[c]thiophen-5-yl]-1,3,4-oxadiazol-2-ol

10 (6) 5-[6-(2-Chloro-4-iodo-phenylamino)-2-oxo-2,3-dihydro-1H-2\$!>4\_-2,1,3-benzothiadiazol-5-yl]-1,3,4-oxadiazol-2-ol

## Group 25

(1) 5-[2-Amino-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol

15 (2) 5-[6-(4-iodo-phenylamino)-1H-indol-5-yl]-1,3,4-oxadiazol-2-ol

(3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol

(4) 5-[5-(4-iodo-phenylamino)-1H-indol-6-yl]-1,3,4-oxadiazol-2-ol

20 (5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-2,3-dihydro-1H-isoindol-5-yl]-1,3,4-oxadiazol-2-ol

(6) 5-[5-(2-Chloro-4-iodo-phenylamino)-1H-indazol-6-yl]-1,3,4-oxadiazol-2-ol

## Group 26

25 (1) 5-[2-Amino-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol

(2) 5-[6-(4-iodo-phenylamino)-1H-indol-5-yl]-1,3,4-oxadiazol-2-ol

(3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzoxazol-5-yl]-1,3,4-oxadiazol-2-ol

30 (4) 5-[5-(4-iodo-phenylamino)-benzoxazol-6-yl]-1,3,4-oxadiazol-2-ol

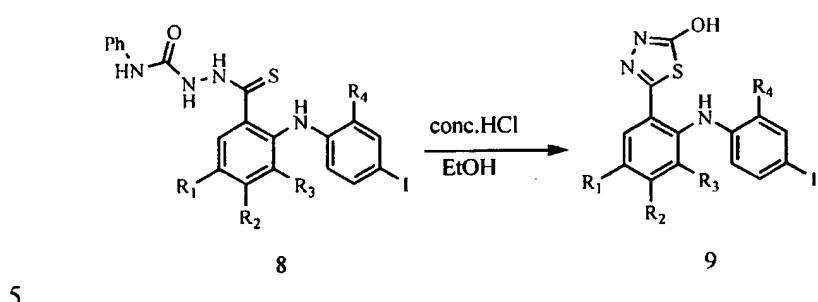
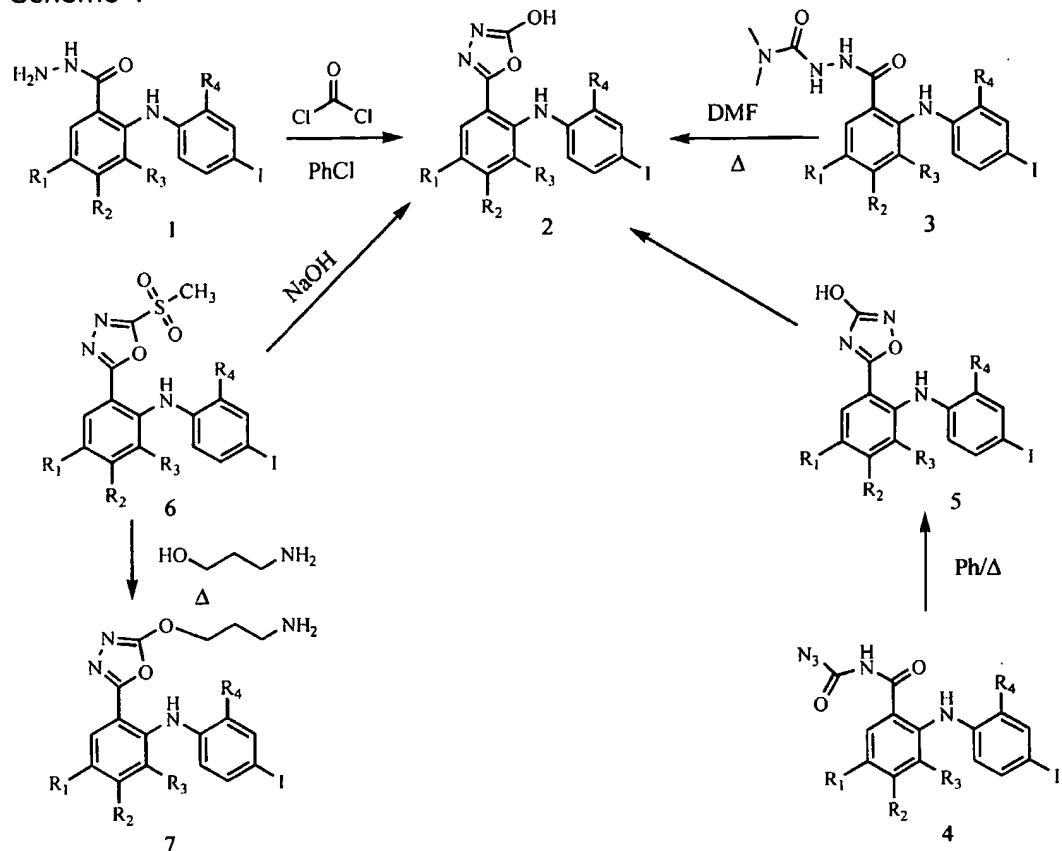
(5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-2,3-dihydro-1H-isoindol-5-yl]-1,3,4-oxadiazol-2-ol

(6) 5-[5-(2-Chloro-4-iodo-phenylamino)-1H-indazol-6-yl]-1,3,4-oxadiazol-2-ol

### C. Synthesis

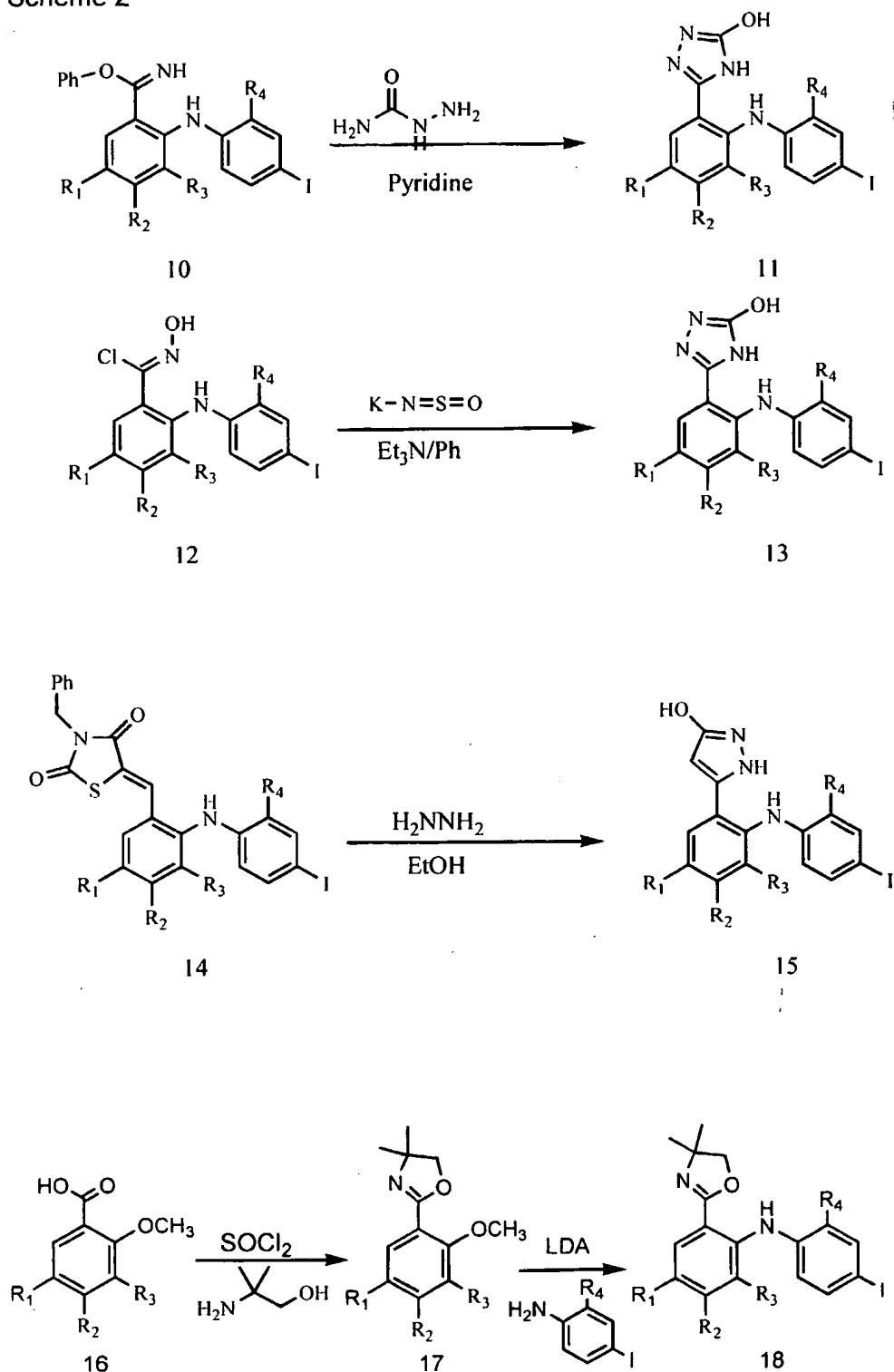
The disclosed compounds can be synthesized according to Schemes 1-25 or analogous variants thereof. These synthetic strategies are further exemplified in Examples 1-8 below. The solvent between compounds 4 and 5 in Scheme 1 is toluene (PhMe).

Scheme 1

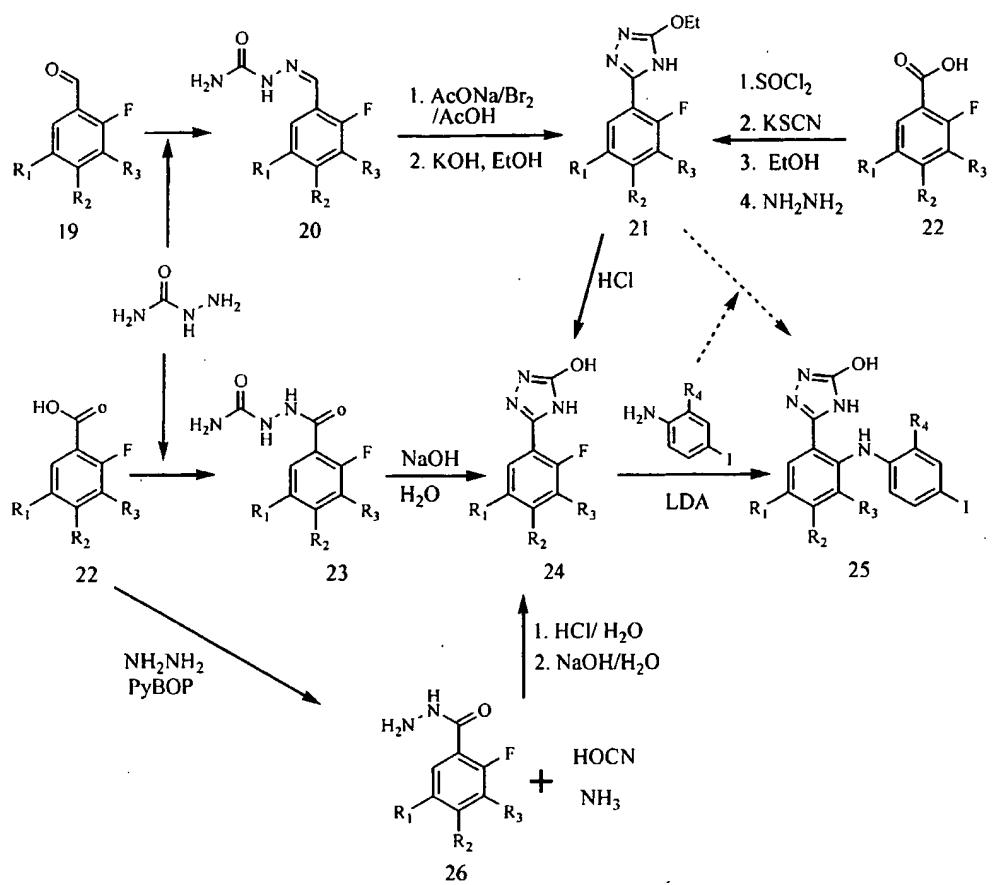


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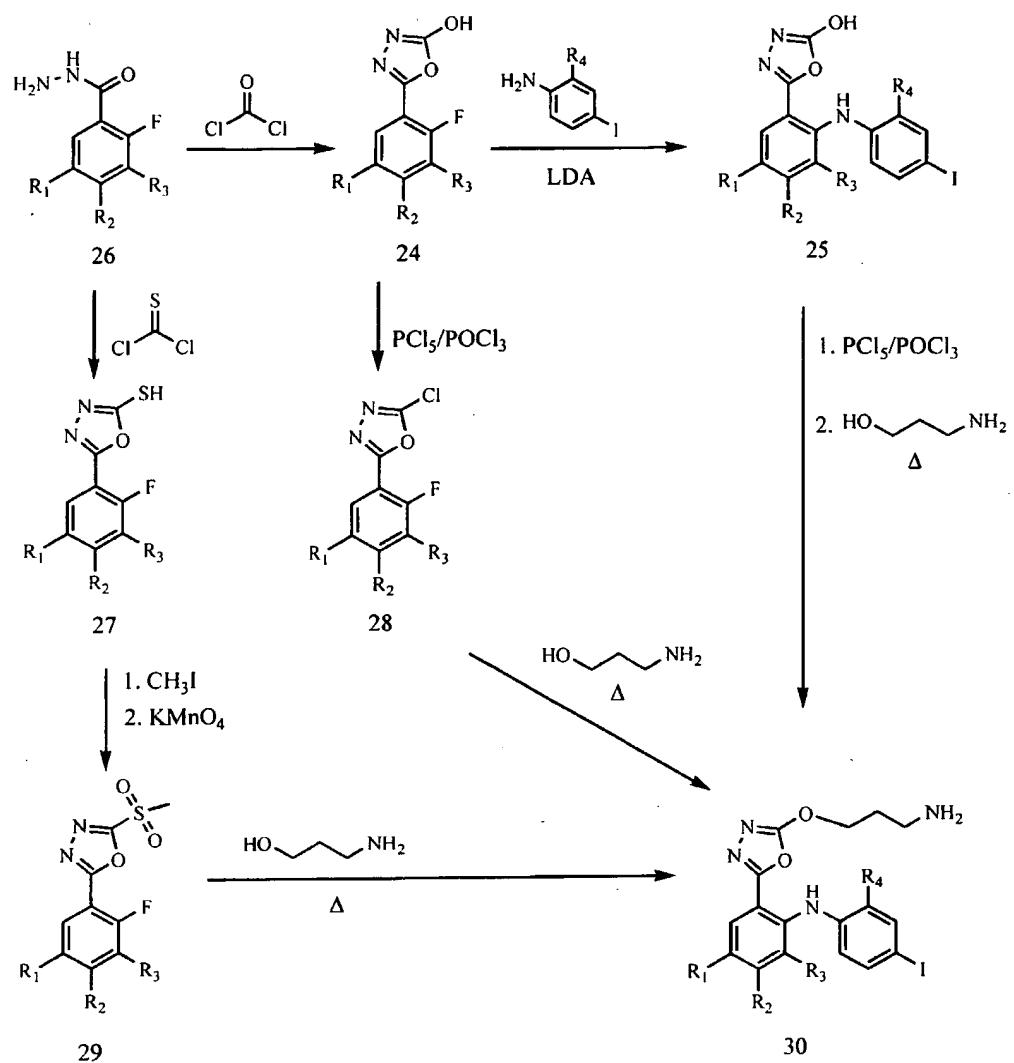
Scheme 2



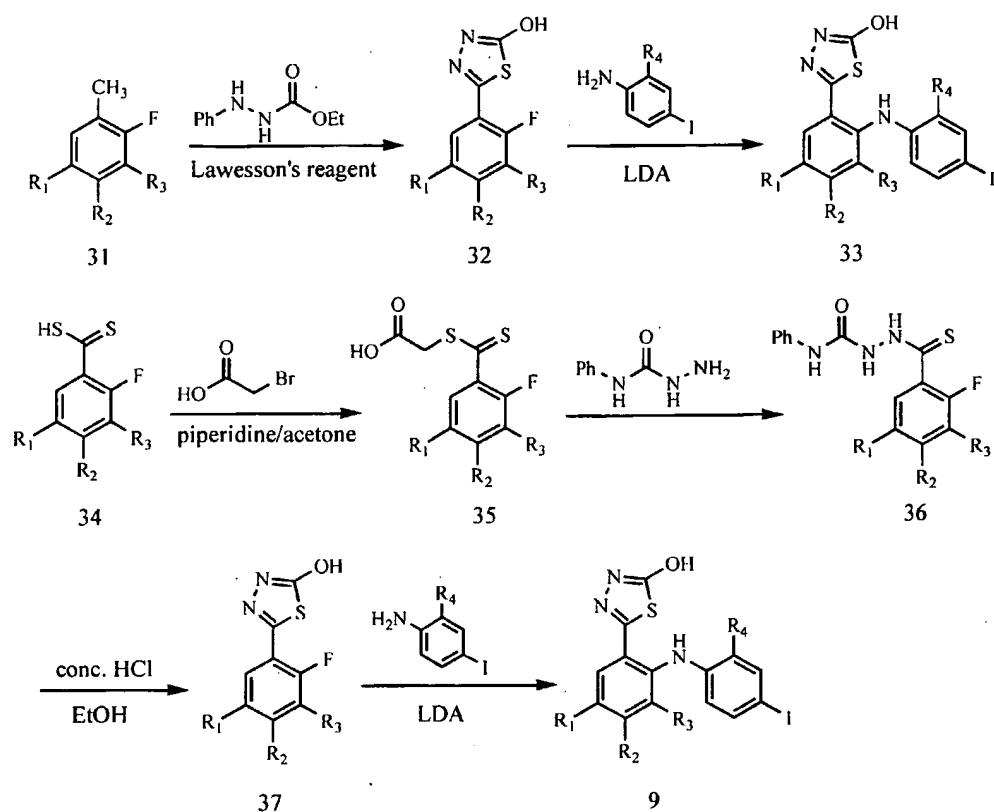
Scheme 3



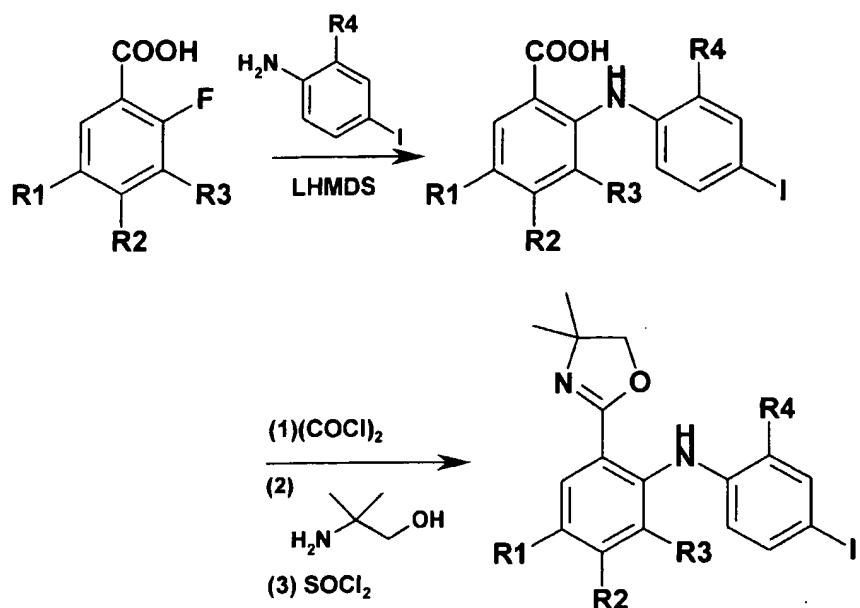
Scheme 4



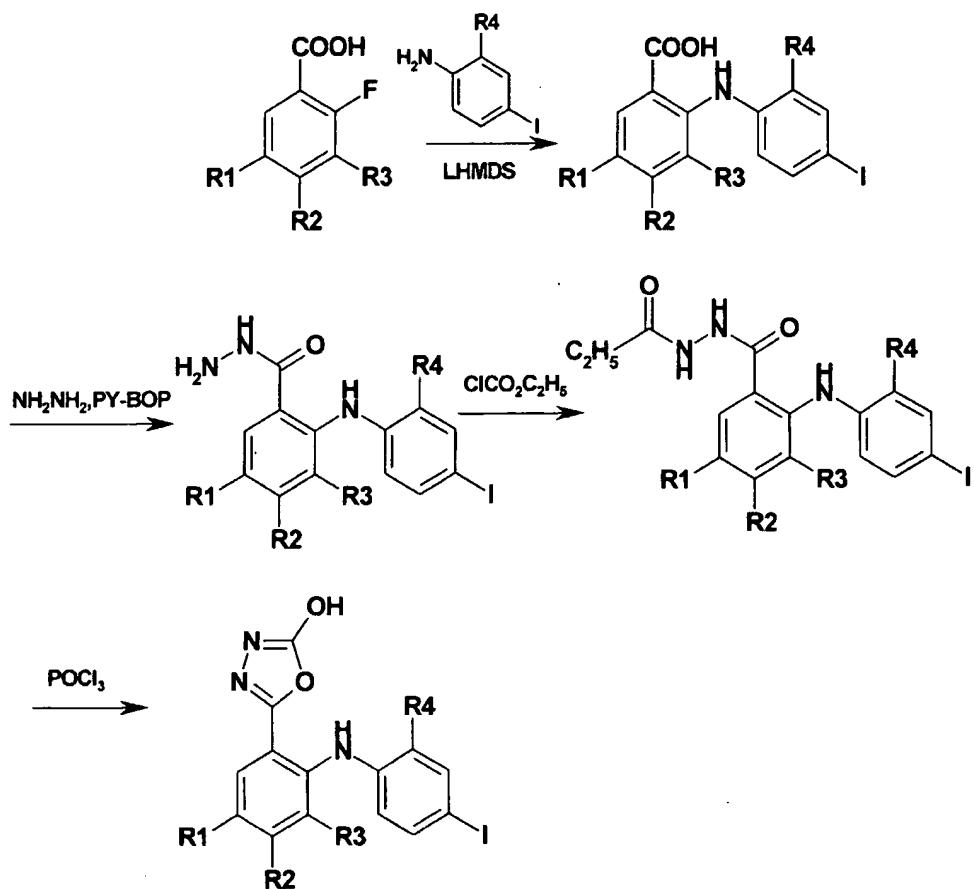
Scheme 5



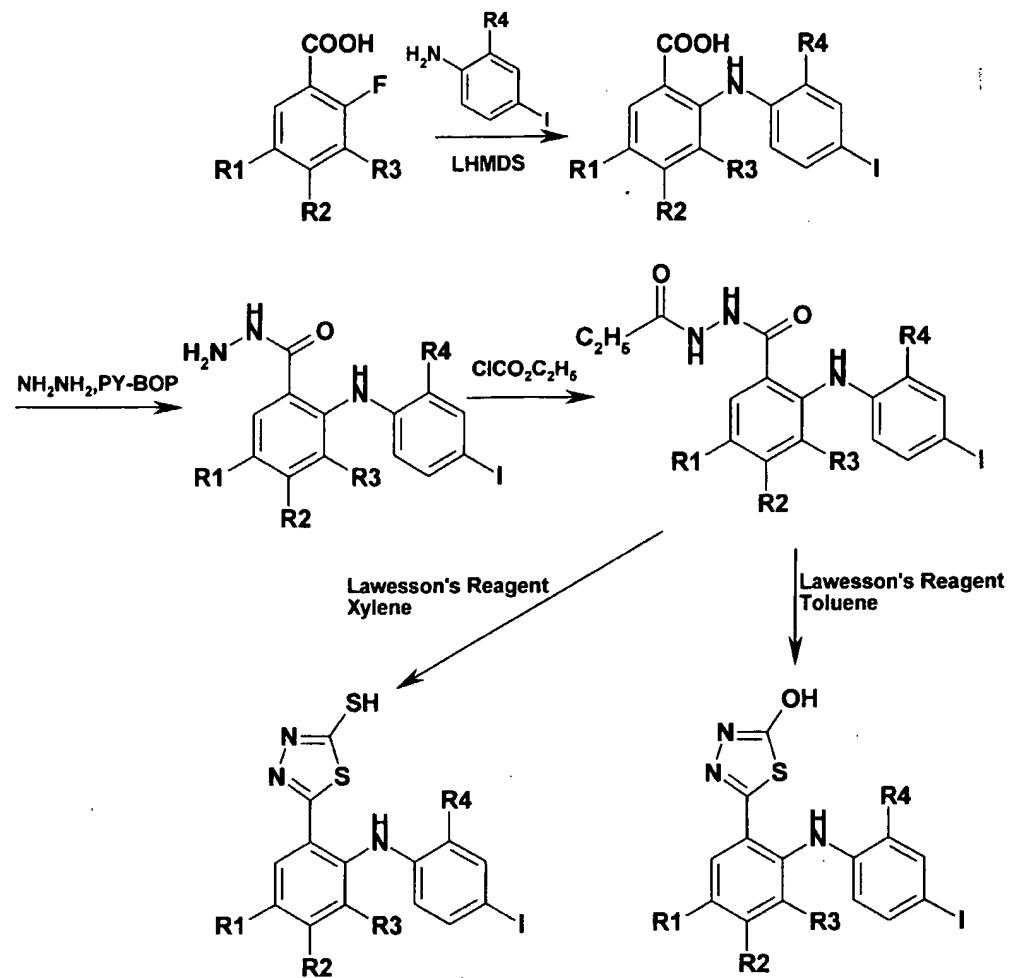
Scheme 6



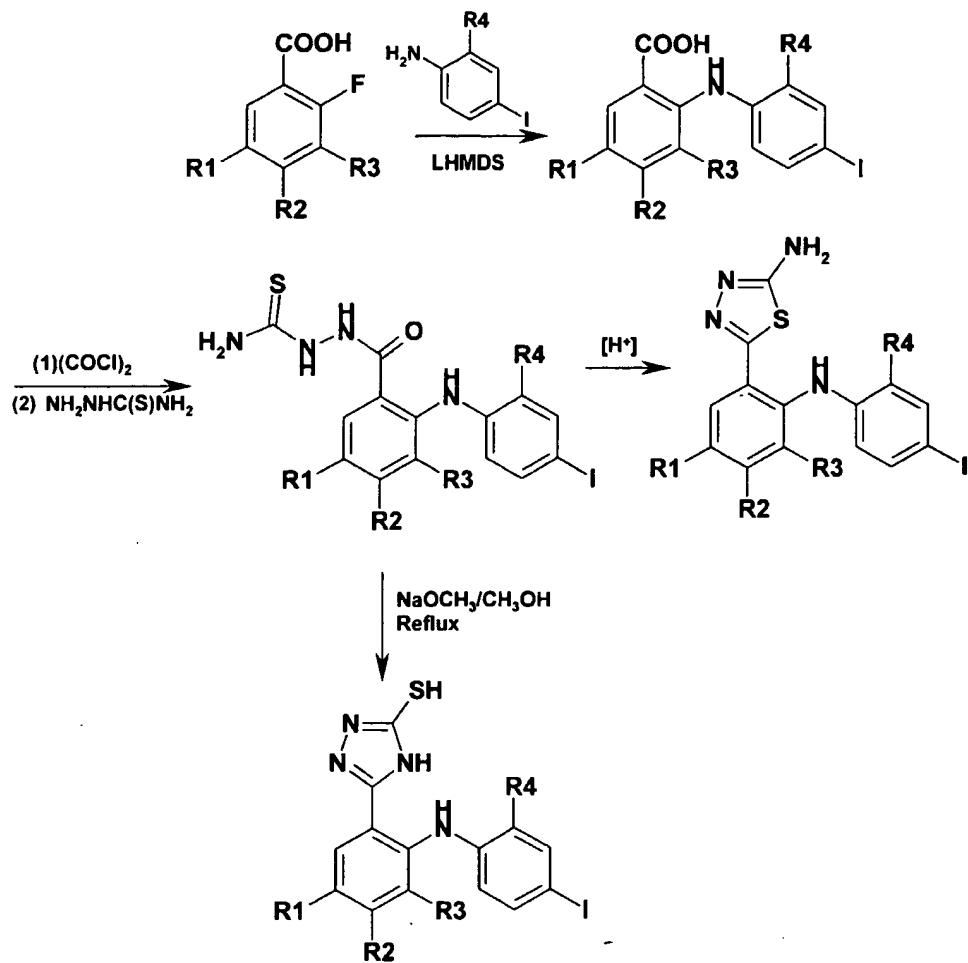
Scheme 7



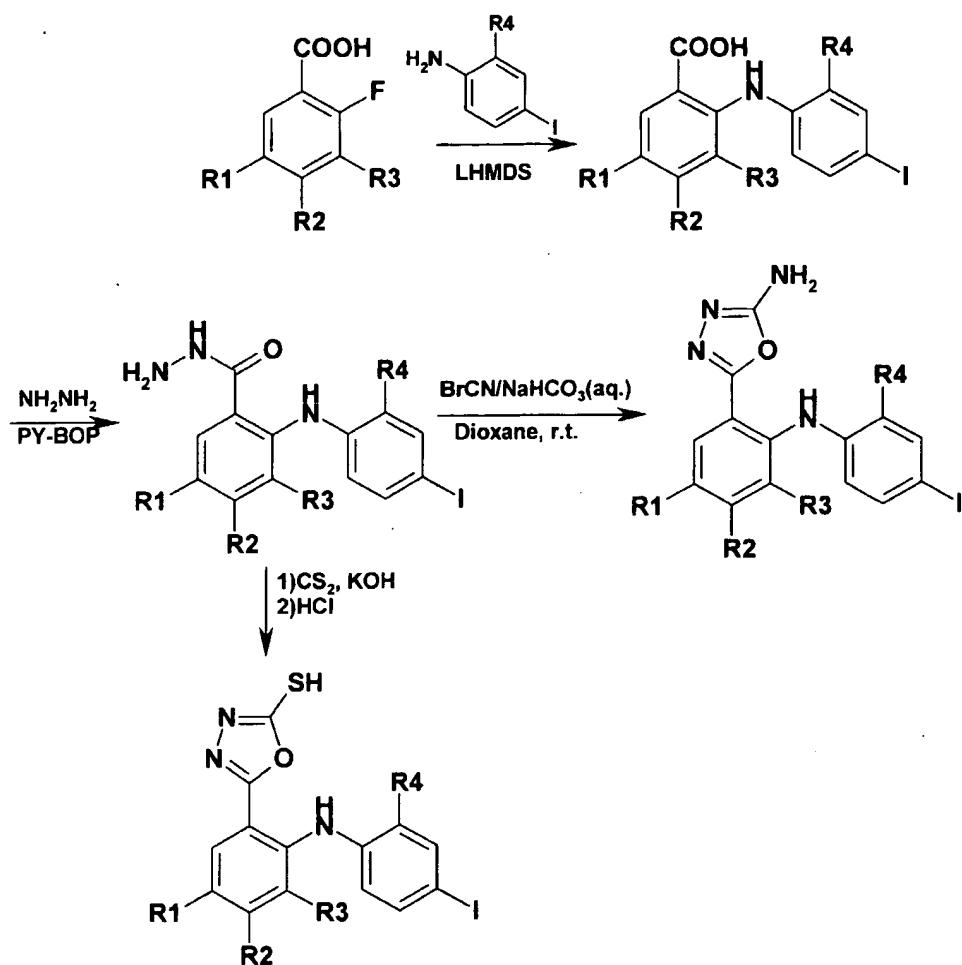
Scheme 8



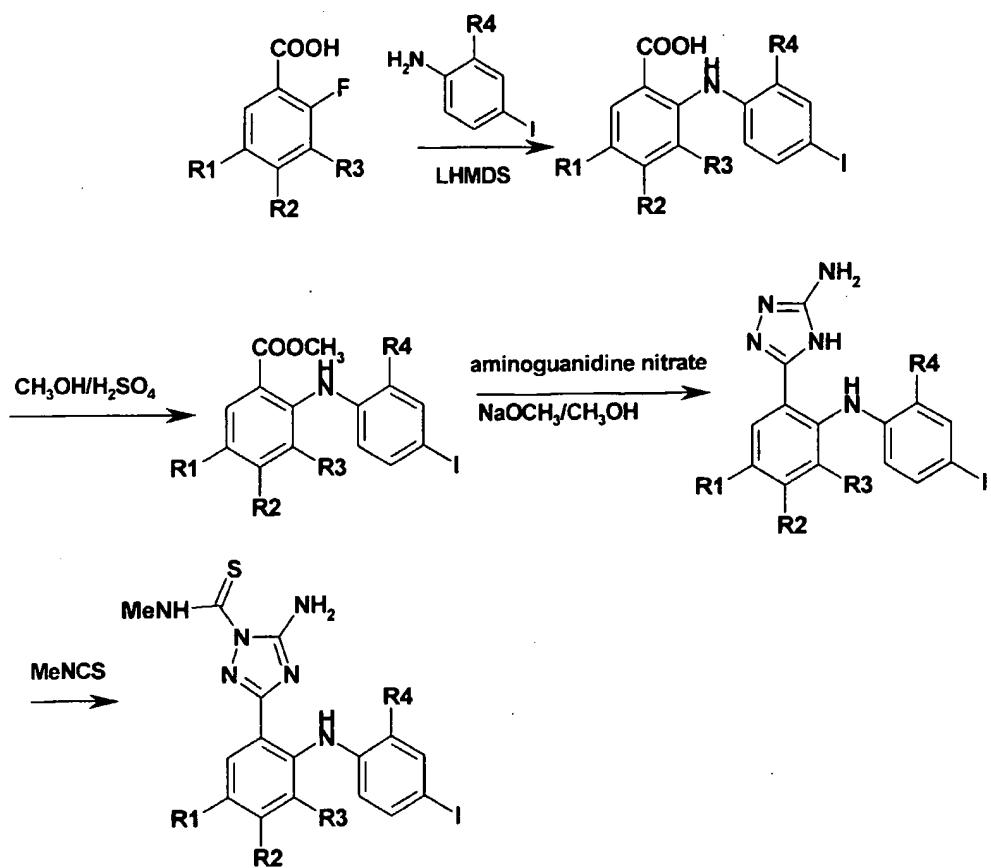
Scheme 9



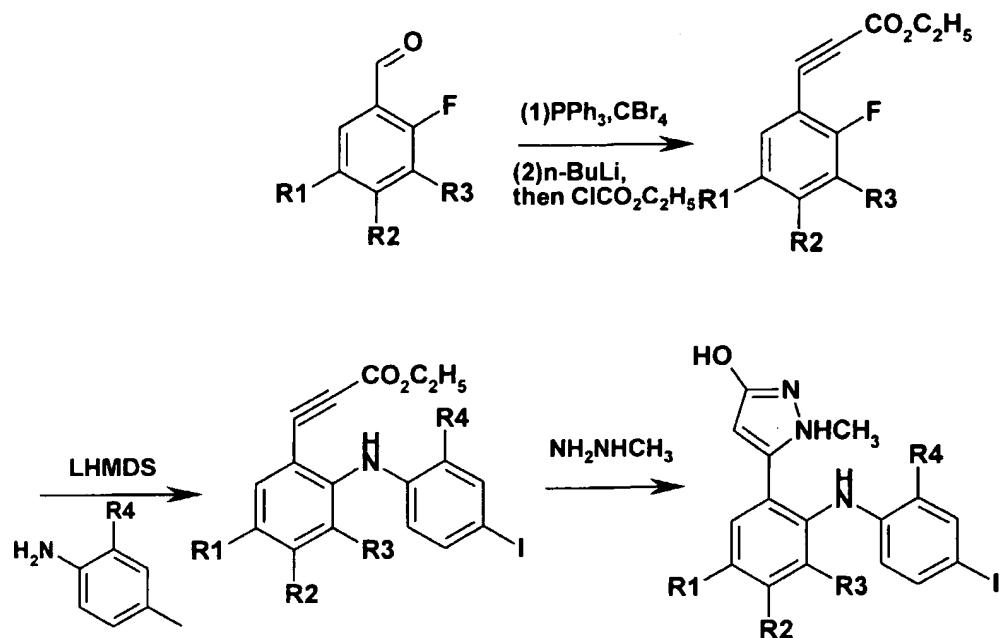
Scheme 10



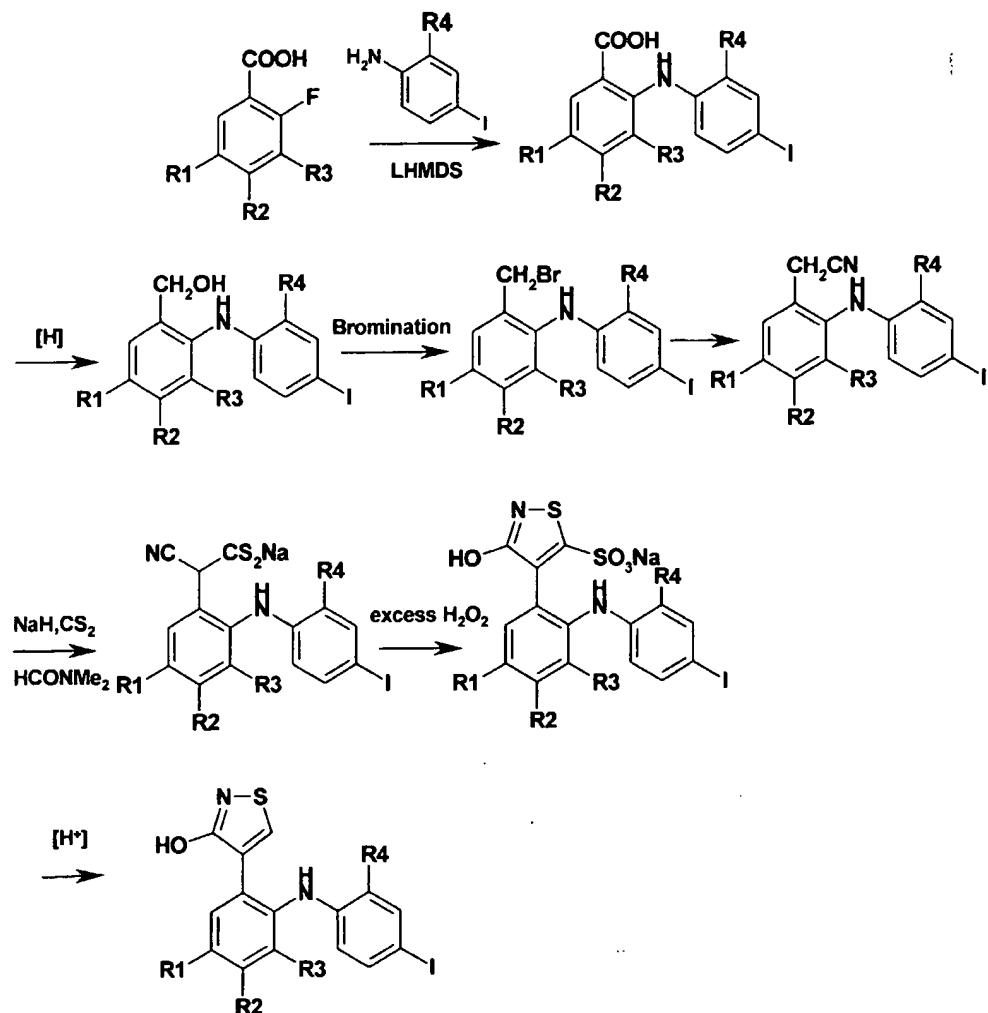
Scheme 11



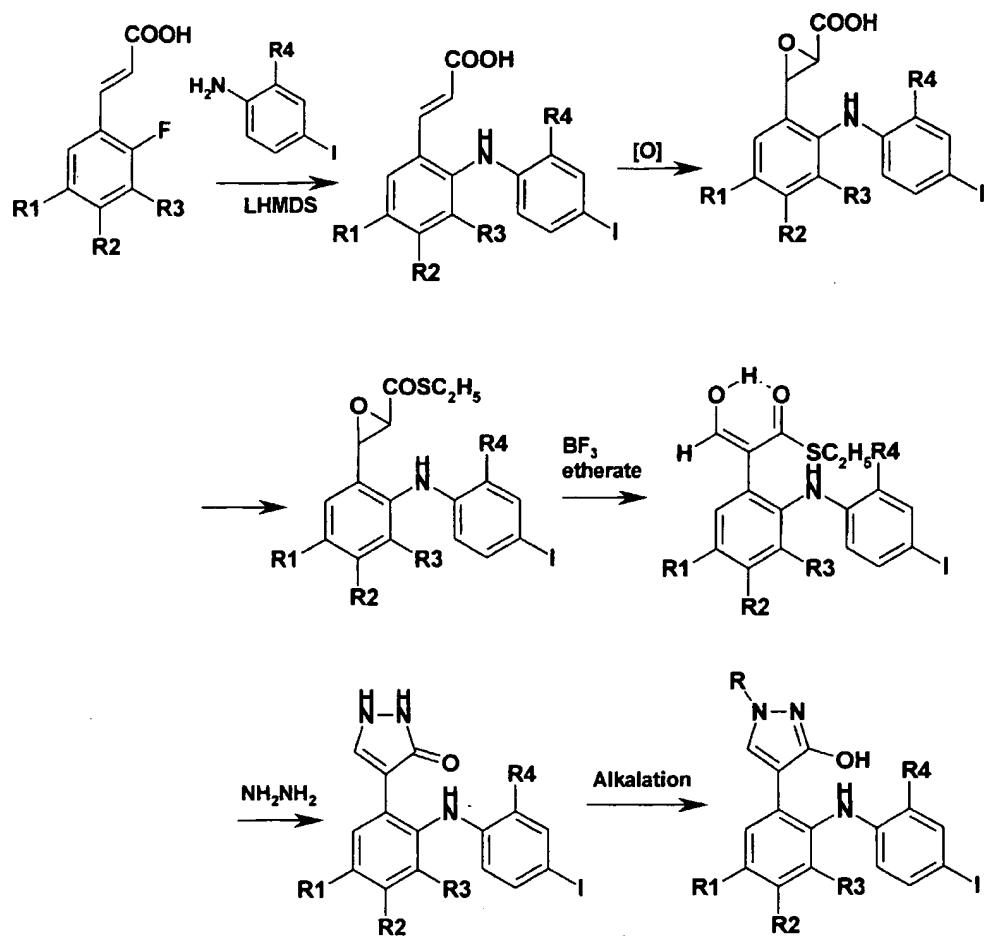
Scheme 12



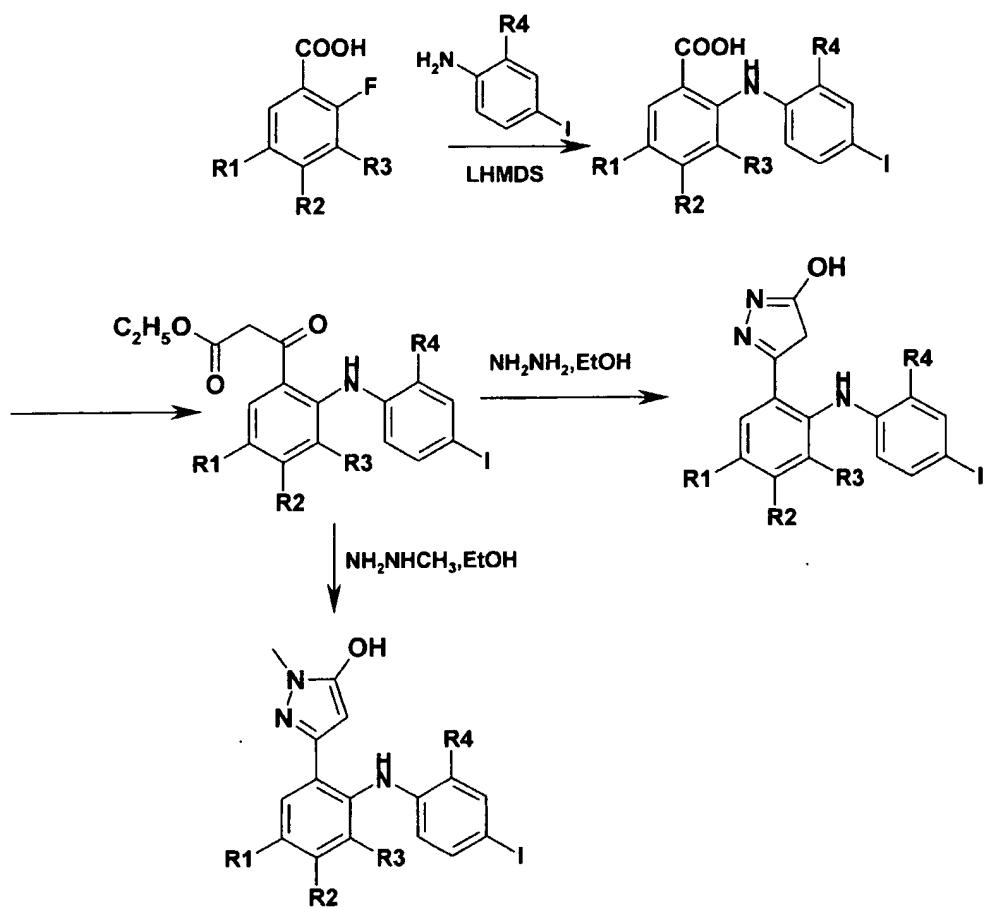
Scheme 13



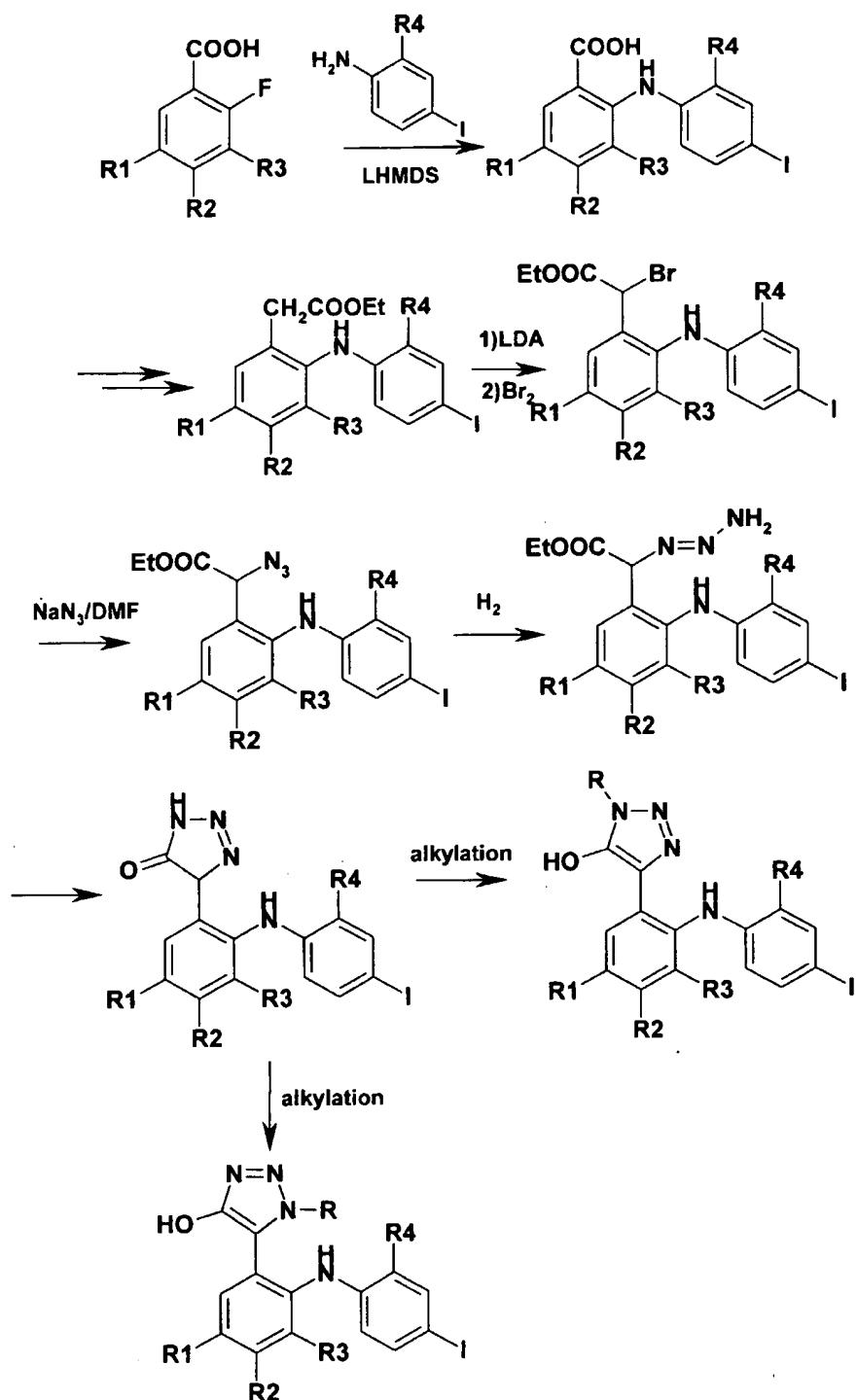
Scheme 14



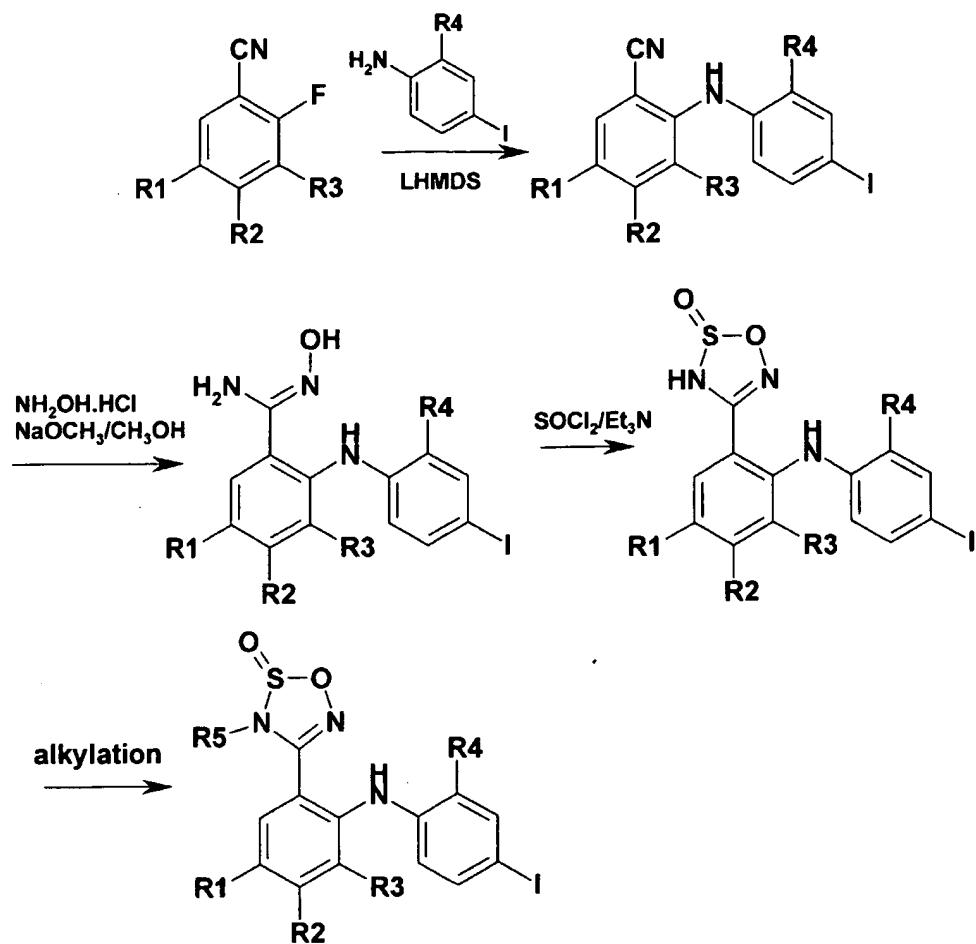
Scheme 15



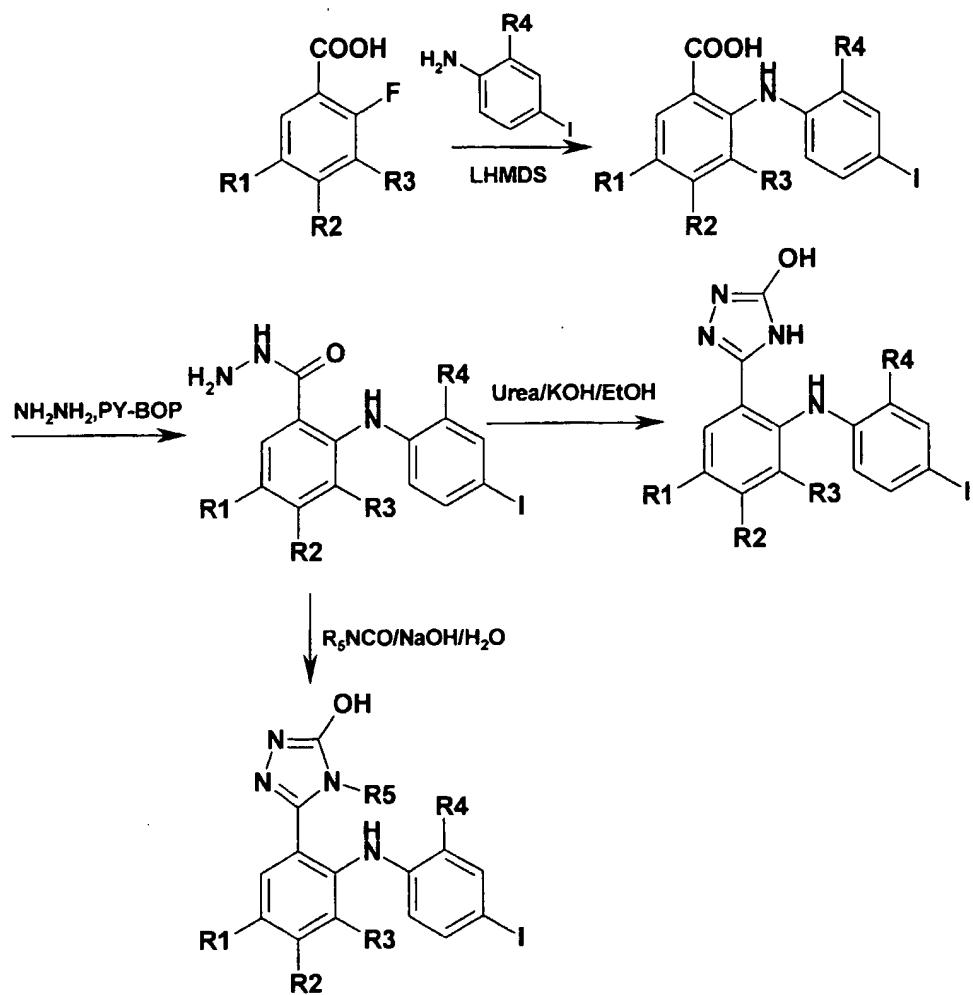
Scheme 16



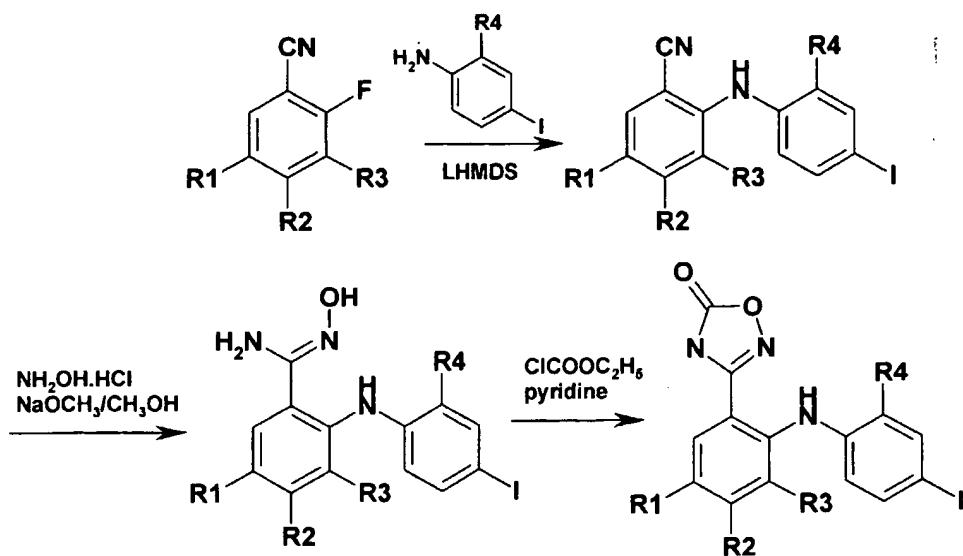
Scheme 17



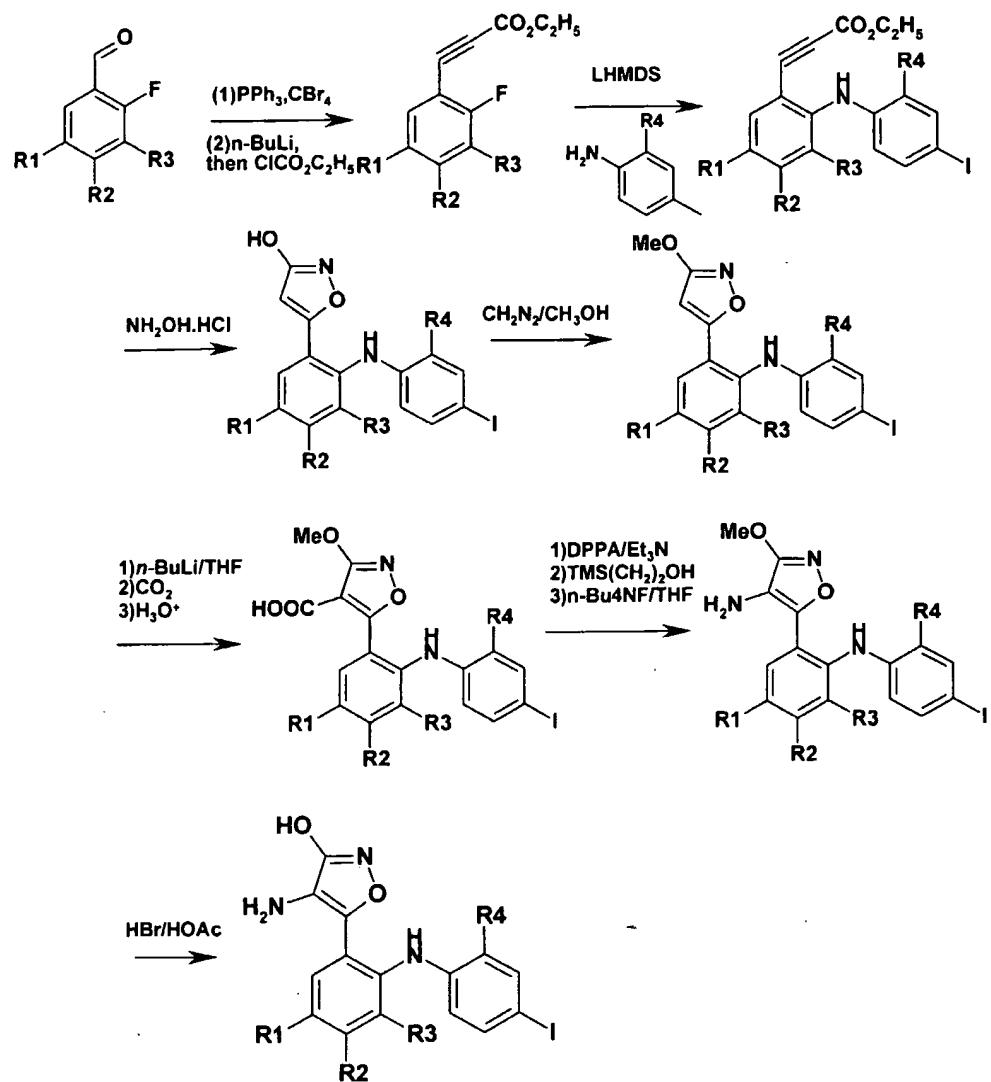
Scheme 18



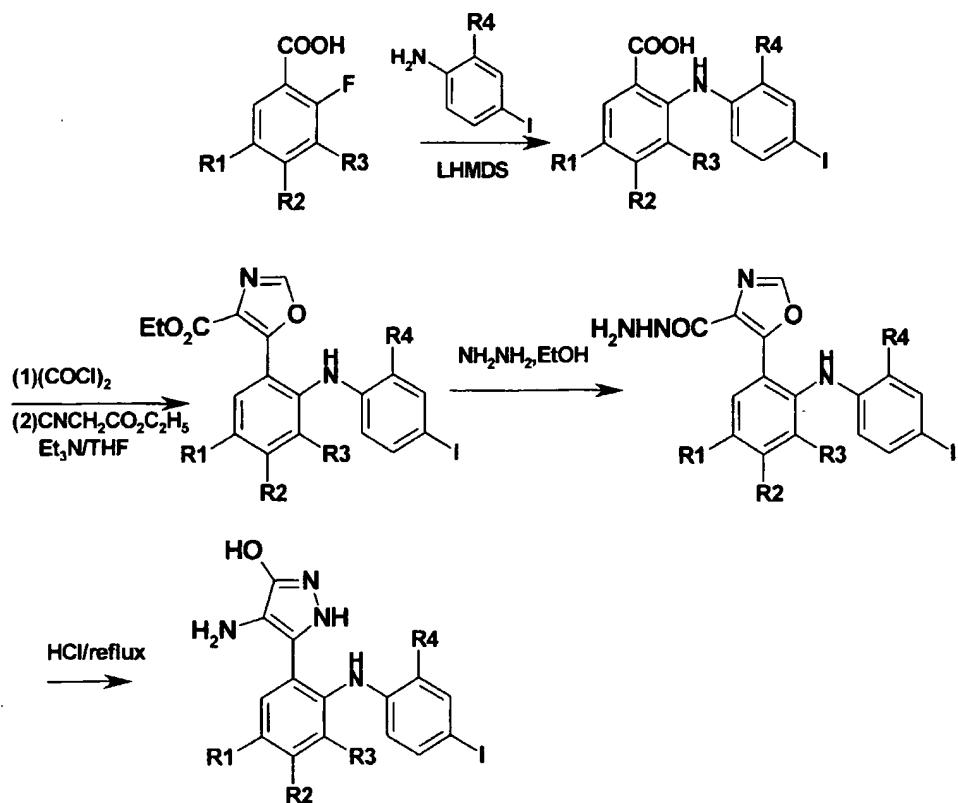
Scheme 19



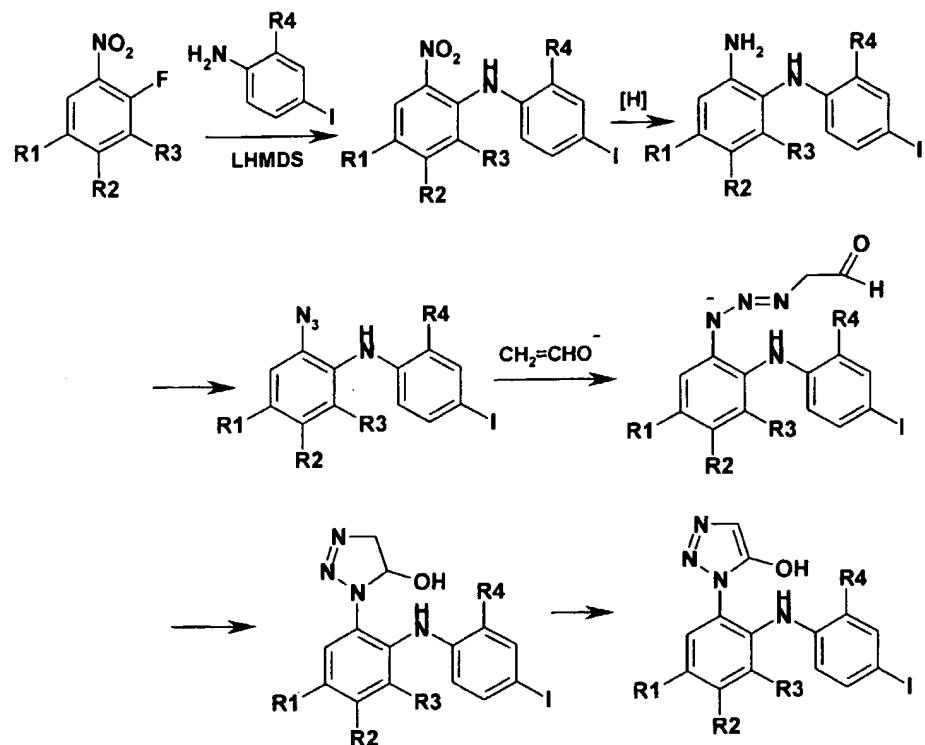
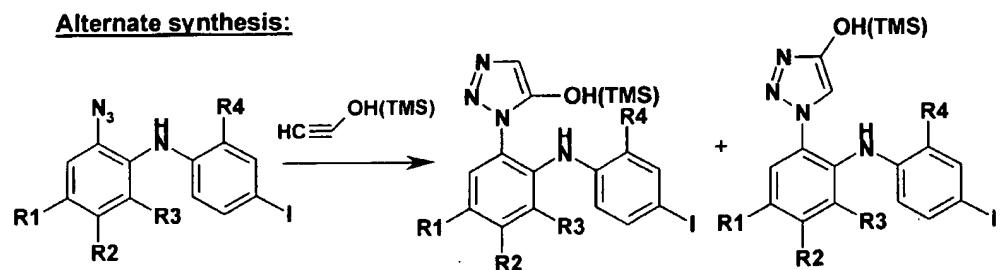
Scheme 20



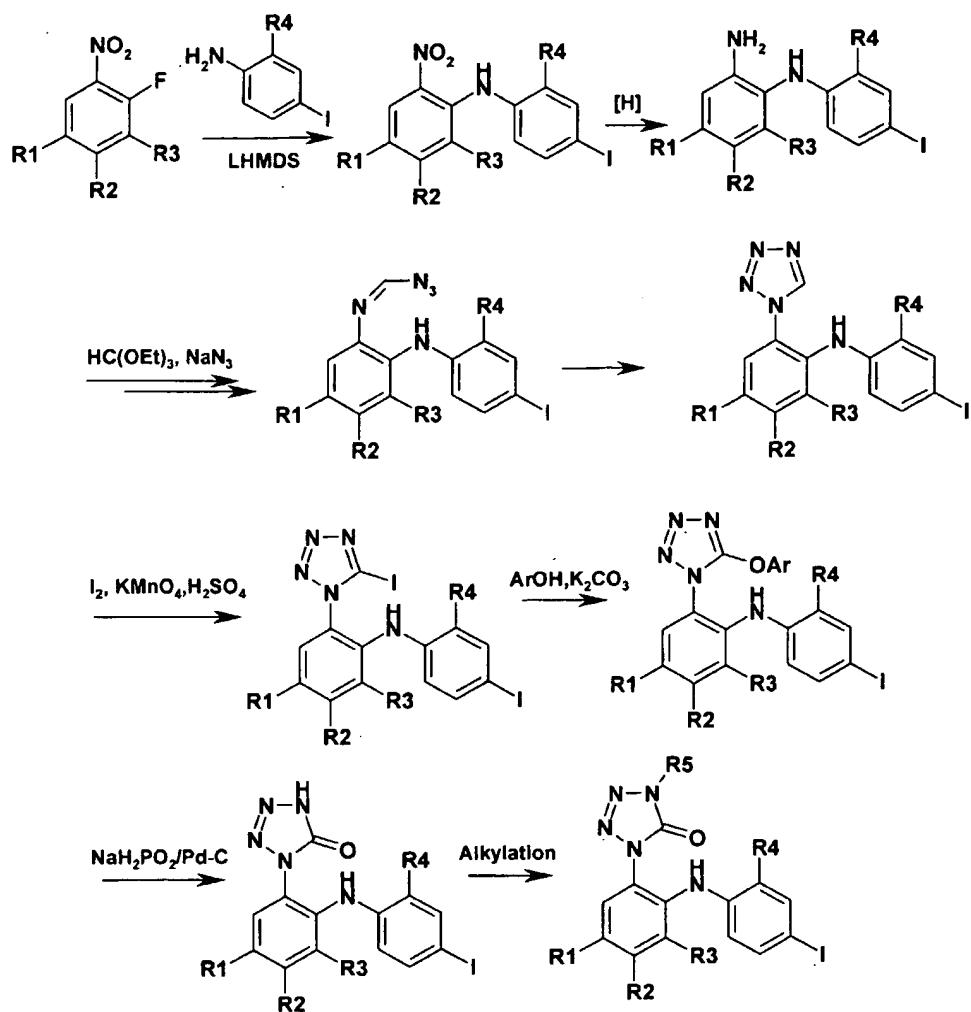
Scheme 21



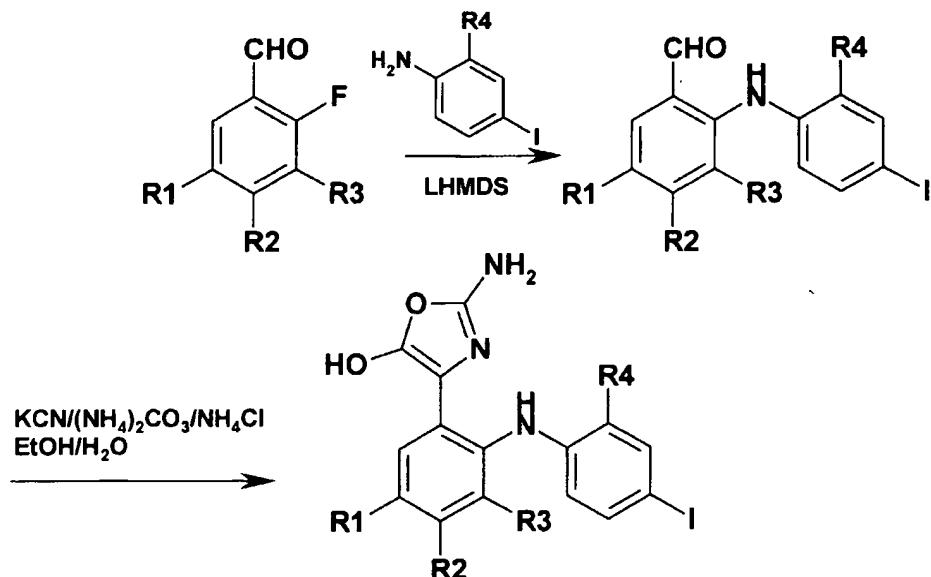
Scheme 22

Alternate synthesis:

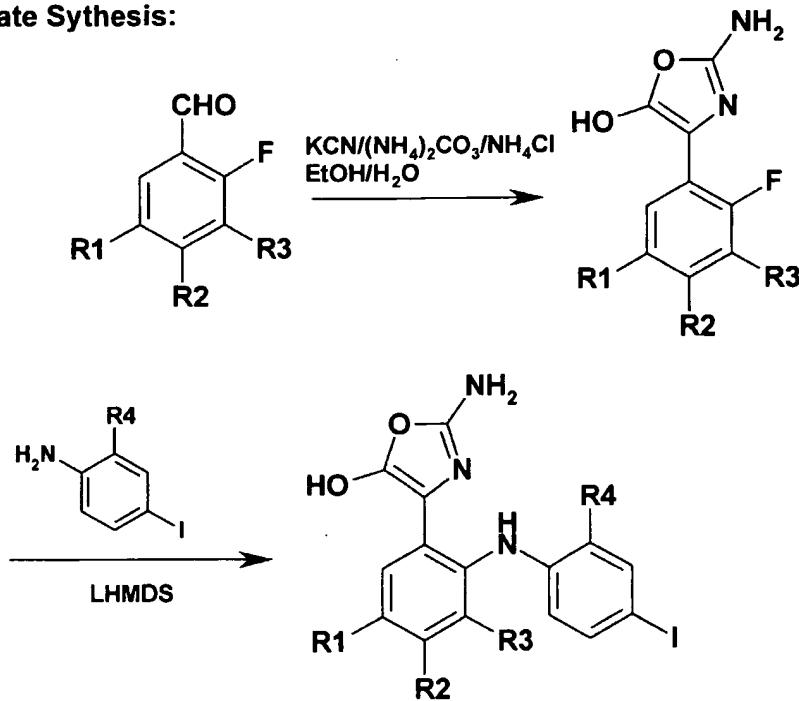
Scheme 23



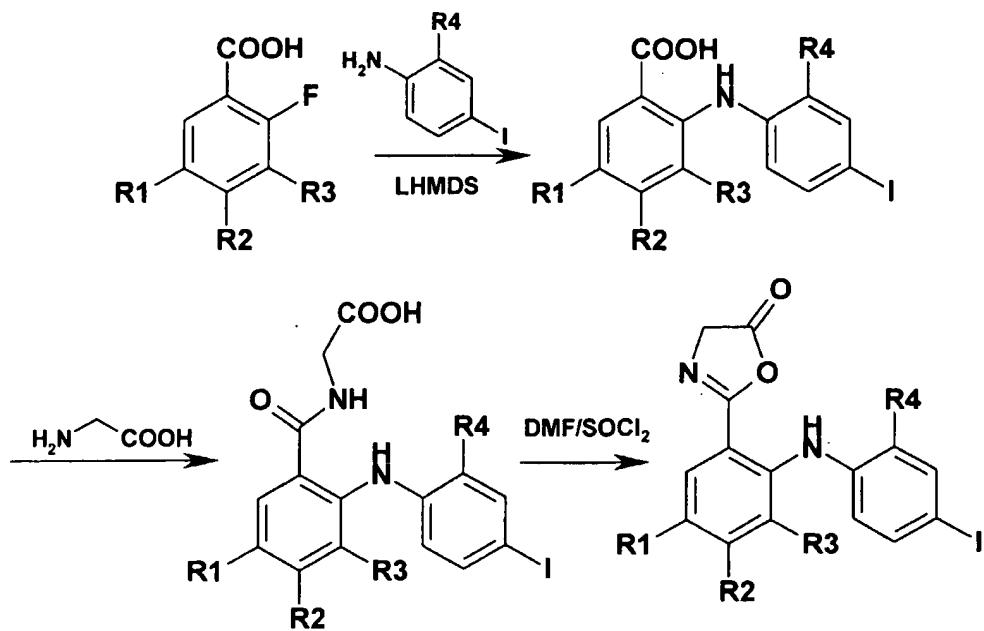
Scheme 24



## Alternate Synthesis:



Scheme 25



#### D. Uses

The disclosed compositions are useful as both prophylactic and therapeutic treatments for diseases or conditions relating to chronic pain, 5 including neuropathic pain, as provided in the Summary section, as well as diseases or conditions modulated by the MEK cascade. For example, in one embodiment, the disclosed method relates to postoperative pain, phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma, 10 vasculitis, crush injury, constriction injury, tissue injury, post-surgical pain, arthritis pain, or limb amputation

For example, local injuries can be treated with local or topical administration. Chronic pain affecting the entire body, such as diabetic neuropathy can be treated with systemic administration (injection or orally) of 15 a disclosed composition. Treatment for chronic pain (e.g., post-operative pain) confined to the lower body can be administered centrally, e.g., epidurally. Formulations and methods of administration can include the use of more than one MEK inhibitor, or a combination of a MEK inhibitor and another pharmaceutical agent, such as an anti-inflammatory, analgesic, muscle 20 relaxing, or anti-infective agent. Preferred routes of administration are oral, intrathecal or epidural, subcutaneous, intravenous, intramuscular, and, for non-human mammals, intraplantar, and are preferably epidural.

##### 1. Dosages

25 Those skilled in the art will be able to determine, according to known methods, the appropriate dosage for a patient, taking into account factors such as age, weight, general health, the type of pain requiring treatment, and the presence of other medications. In general, an effective amount will be between 0.1 and 1000 mg/kg per day, preferably between 1 and 300 mg/kg 30 body weight, and daily dosages will be between 10 and 5000 mg for an adult subject of normal weight. Commercially available capsules or other

formulations (such as liquids and film-coated tablets) of 100 mg, 200 mg, 300 mg, or 400 mg can be administered according to the disclosed methods.

## 2. Formulations

5 Dosage unit forms include tablets, capsules, pills, powders, granules, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers adapted for subdivision into individual doses. Dosage unit forms can also be adapted for various methods of administration, including controlled release formulations, such as subcutaneous implants.

10 Administration methods include oral, rectal, parenteral (intravenous, intramuscular, subcutaneous), intracisternal, intravaginal, intraperitoneal, intravesical, local (drops, powders, ointments, gels, or cream), and by inhalation (a buccal or nasal spray).

15 Parenteral formulations include pharmaceutically acceptable aqueous or nonaqueous solutions, dispersion, suspensions, emulsions, and sterile powders for the preparation thereof. Examples of carriers include water, ethanol, polyols (propylene glycol, polyethylene glycol), vegetable oils, and injectable organic esters such as ethyl oleate. Fluidity can be maintained by the use of a coating such as lecithin, a surfactant, or maintaining appropriate 20 particle size. Carriers for solid dosage forms include (a) fillers or extenders, (b) binders, (c) humectants, (d) disintegrating agents, (e) solution retarders, (f) absorption accelerators, (g) adsorbants, (h) lubricants, (i) buffering agents, and (j) propellants.

25 Compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents; antimicrobial agents such as parabens, chlorobutanol, phenol, and sorbic acid; isotonic agents such as a sugar or sodium chloride; absorption-prolonging agents such as aluminum monostearate and gelatin; and absorption-enhancing agents.

### 3. Related compounds

The invention provides the disclosed compounds and closely related, pharmaceutically acceptable forms of the disclosed compounds, such as salts, esters, amides, hydrates or solvated forms thereof; masked or protected forms; and racemic mixtures, or enantiomerically or optically pure forms.

Pharmaceutically acceptable salts, esters, and amides include carboxylate salts (e.g., C<sub>1-8</sub> alkyl, cycloalkyl, aryl, heteroaryl, or non-aromatic heterocyclic), amino acid addition salts, esters, and amides which are within a reasonable benefit/risk ratio, pharmacologically effective, and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. Representative salts include hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulfonate. These may include alkali metal and alkali earth cations such as sodium, potassium, calcium, and magnesium, as well as non-toxic ammonium, quaternary ammonium, and amine cations such as tetramethyl ammonium, methylamine, trimethylamine, and ethylamine. See, for example, S.M. Berge, et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977, 66:1-19 which is incorporated herein by reference. Representative pharmaceutically acceptable amides of the invention include those derived from ammonia, primary C<sub>1-6</sub> alkyl amines and secondary di (C<sub>1-6</sub> alkyl) amines. Secondary amines include 5- or 6-membered heterocyclic or heteroaromatic ring moieties containing at least one nitrogen atom and optionally between 1 and 2 additional heteroatoms. Preferred amides are derived from ammonia, C<sub>1-3</sub> alkyl primary amines, and di (C<sub>1-2</sub> alkyl)amines. Representative pharmaceutically acceptable esters of the invention include C<sub>1-7</sub> alkyl, C<sub>5-7</sub> cycloalkyl, phenyl, and phenyl(C<sub>1-6</sub>)alkyl esters. Preferred esters include methyl esters.

The invention also includes disclosed compounds having one or more functional groups (e.g., hydroxyl, amino, or carboxyl) masked by a protecting group. Some of these masked or protected compounds are pharmaceutically

acceptable; others will be useful as intermediates. Synthetic intermediates and processes disclosed herein, and minor modifications thereof, are also within the scope of the invention.

## 5 HYDROXYL PROTECTING GROUPS

Hydroxyl protecting groups include: ethers, esters, and protection for 1,2- and 1,3-diols. The ether protecting groups include: methyl, substituted methyl ethers, substituted ethyl ethers, substituted benzyl ethers, silyl ethers and conversion of silyl ethers to other functional groups.

### 10 Substituted Methyl Ethers

Substituted methyl ethers include: methoxymethyl, methylthiomethyl, *t*-utylthiomethyl, (phenyldimethylsilyl) methoxymethyl, benzyloxymethyl, *p*-ethoxybenzyloxymethyl, (4-methoxyphenoxy) methyl, guaiacolmethyl, *t*-butoxymethyl, 4-pentyloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloro- ethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl, tetrahydropyranyl, 3-bromotetrahydro-pyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothio-pyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxido, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, and 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-ethanobenzofuran-2-yl.

### Substituted Ethyl Ethers

Substituted ethyl ethers include: 1-ethoxyethyl, 1-(2, chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilyethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, and benzyl.

### Substituted Benzyl Ethers

Substituted benzyl ethers include: *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2- and 4-picoly, 3-methyl-2-picoly N-oxido, diphenylmethyl, *p*, *p*'-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl,  $\alpha$ -naphthylidiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl,

tri-(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)phenyldiphenylmethyl, 4,4',4"-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-tris(levulinoxyloxyphenyl) methyl, 4,4',4"tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-ylmethyl)bis(4',4"-dimethoxyphenyl)-methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl) xanthenyl, 9-(9-phenyl-10-oxo) anthryl, 1,3-benzodithiolan-2-yl, and benzisothiazolyl S,S-dioxido.

#### Silyl Ethers

Silyl ethers include: trimethylsilyl, triethylsilyl, triisopropylsilyl, 10 dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethysilyl, and *t*-butylmethoxyphenylsilyl.

#### ESTERS

15 Esters protecting groups include: esters, carbonates, assisted cleavage, miscellaneous esters, and sulfonates.

#### Esters

Examples of protective esters include: formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, 20 methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, *p*-P-phenylacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio) pentanoate, pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, and 2,4,6-trimethylbenzoate (mesitoate).

25 Carbonates

Carbonates include: methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl) ethyl, 2-(phenylsulfonyl) ethyl, 2-(triphenylphosphonio) ethyl, isobutyl, vinyl, allyl, *p*-nitrophenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, S-benzyl thiocarbonate, 4-ethoxy-1-naphthyl, and methyl dithiocarbonate.

### Assisted Cleavage

Examples of assisted cleavage protecting groups include: 2-iodobenzoate, 4-azido-butyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl) benzoate, 2-formylbenzene-sulfonate, 2-(methylthiomethoxy) ethyl carbonate, 4-(methylthiomethoxymethyl) benzoate, and 2-(methylthiomethoxymethyl) benzoate.

### Miscellaneous Esters

In addition to the above classes, miscellaneous esters include: 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl) phenoxyacetate, 2,4-bis(1,1-dimethylpropyl) phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinate, (*E*)-2-methyl-2-butenoate (tiglate), *o*-(methoxycarbonyl) benzoate, *p*-P-benzoate,  $\alpha$ -naphthoate, nitrate, alkyl *N,N,N*'-*N*'-tetramethylphosphorodiamide, *N*-phenylcarbamate, borate, dimethylphosphinothioyl, and 2,4-dinitrophenylsulfenate.

### Sulfonates

Protective sulfonates includes: sulfate, methanesulfonate(mesylate), benzylsulfonate, and tosylate.

## 20 PROTECTION FOR 1,2- AND 1,3-DIOLS

The protection for 1,2 and 1,3-diols group includes: cyclic acetals and ketals, cyclic ortho esters, and silyl derivatives.

### Cyclic Acetals and Ketals

Cyclic acetals and ketals include: methylene, ethylidene, 1-*t*-butylethylidene, 1-phenylethylidene, (4-methoxyphenyl) ethylidene, 2,2,2-trichloroethylidene, acetonide (isopropylidene), cyclopentylidene, cyclohexylidene, cycloheptylidene, benzylidene, *p*-methoxybenzylidene, 2,4-dimethoxybenzylidene, 3,4-dimethoxybenzylidene, and 2-nitrobenzylidene.

### Cyclic Ortho Esters

Cyclic ortho esters include: methoxymethylene, ethoxymethylene, dimethoxymethylene, 1-methoxyethylidene, 1-ethoxyethylidene, 1,2-dimethoxyethylidene,

$\alpha$ -methoxybenzylidene, 1-(*N,N*-dimethylamino)ethylidene derivative,  $\alpha$ -(*N,N*-dimethylamino) benzylidene derivative, and 2-oxacyclopentylidene.

## 5 PROTECTION FOR THE CARBOXYL GROUP

### ESTERS

Ester protecting groups include: esters, substituted methyl esters, 2-substituted ethyl esters, substituted benzyl esters, silyl esters, activated esters, miscellaneous derivatives, and stannyl esters.

#### 10 Substituted Methyl Esters

Substituted methyl esters include: 9-fluorenylmethyl, methoxymethyl, methylthiomethyl, tetrahydropyranyl, tetrahydrofuranyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxy-methyl, benzyloxymethyl, phenacyl, *p*-bromophenacyl,  $\alpha$ -methylphenacyl, *p*-methoxyphenacyl, carboxamidomethyl, and *N*-

#### 15 phthalimidomethyl.

#### 2-Substituted Ethyl Esters

2-Substituted ethyl esters include: 2,2,2-trichloroethyl, 2-haloethyl, *i*-chloroalkyl, 2-(trimethylsilyl)ethyl, 2-methylthioethyl, 1,3-dithianyl-2-methyl, 2(*p*-nitrophenylsulfonyl)-ethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(2'-pyridyl)ethyl, 2-20 (diphenylphosphino)ethyl, 1-methyl-1-phenylethyl, *t*-butyl, cyclopentyl, cyclohexyl, allyl, 3-buten-1-yl, 4-(trimethylsilyl)-2-buten-1-yl, cinnamyl,  $\alpha$ -methylcinnamyl, phenyl, *p*-(methylmercapto)-phenyl, and benzyl.

#### Substituted Benzyl Esters

Substituted benzyl esters include: triphenylmethyl, diphenylmethyl, bis(*o*-nitrophenyl)methyl, 9-anthrylmethyl, 2-(9,10-dioxo)anthrylmethyl, 5-dibenzo-suberyl, 1-pyrenylmethyl, 2-(trifluoromethyl)-6-chromylmethyl, 2,4,6-trimethylbenzyl, *p*-bromobenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, 4-(methylsulfinyl)benzyl, 4-sulfonylbenzyl, piperonyl, and 4-P-benzyl.

#### 30 Silyl Esters

Silyl esters include: trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, *i*-propyldimethylsilyl, phenyldimethylsilyl, and di- *t*-butyldimethylsilyl.

### Miscellaneous Derivatives

Miscellaneous derivatives includes: oxazoles, 2-alkyl-1,3-oxazolines, 4-alkyl-5-oxo-1,3-oxazolidines, 5-alkyl-4-oxo-1,3-dioxolanes, ortho esters, phenyl group, and pentaaminocobalt(III) complex.

5        Stanny Esters

Examples of stanny esters include: triethylstanny and tri-*n*-butylstanny.

### AMIDES AND HYDRAZIDES

Amides include: *N,N* -dimethyl, pyrrolidinyl, piperidinyl, 5,6-dihydrophenanthridinyl, *o*-nitroanilides, *N*-7-nitroindolyl, *N*-8-nitro-1,2,3,4-tetrahydroquinolyl, and *p*-P-benzenesulfonamides. Hydrazides include: *N*-phenyl, *N,N* '-diisopropyl and other dialkyl hydrazides.

### PROTECTION FOR THE AMINO GROUP

15

#### CARBAMATES

Carbamates include: carbamates, substituted ethyl, assisted cleavage, photolytic cleavage, urea-type derivatives, and miscellaneous carbamates.

##### Carbamates

20 Carbamates include: methyl and ethyl, 9-fluorenylmethyl, 9-(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydro- thioxanthyl)]methyl, and 4-methoxyphenacyl.

##### Substituted Ethyl

Substituted ethyl protective groups include: 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'-and 4'-pyridyl)ethyl, 2-(*N,N*-cyclohexylcarboxamido)- ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, connamyl, 4-nitrocinnamyl, quinolyl, *N*-hydroxypiperidinyl, alkyldithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, and diphenylmethyl.

Assisted Cleavage

Protection via assisted cleavage includes: 2-methylthioethyl, 2-methylsulfonyleethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 5 4-methylthiophenyl, 2,4-dimethyl-thiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2cyanoethyl, *m*-chloro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolyl-methyl, and 2-(trifluoromethyl)-6-chromonylmethyl.

Photolytic Cleavage

10 Photolytic cleavage methods use groups such as: *m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, and phenyl(*o*-nitrophenyl)methyl.

Urea-Type Derivatives

15 Examples of of urea-type derivatives include: phenothiazinyl-(10)-carbonyl derivative, *N*'-*p*-toluenesulfonylaminocarbonyl, and *N*'-phenylaminothiocarbonyl.

Miscellaneous Carbamates

In addition to the above, miscellaneous carbamates include: *t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, 20 cyclopropylmethyl, *p*-decyloxy-benzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(*N,N*-dimethyl-carboxamido)-benzyl, 1,1-dimethyl-3(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethyl-propynyl, di(2-pyridyl)methyl, 2-furanyl methyl, 2-iodoethyl, isobornyl, isobutyl, isonicotinyl, *p*(*p*'-methoxyphenyl- azo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropyl- methyl, 1-methyl-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1(*p*-henylazophenyl)- ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium) benzyl, and 2,4,6-trimethylbenzyl.

AMIDESAmides

Amides includes: *N*-formyl, *N*-acetyl, *N*-chloroacetyl, *N*-trichloroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridyl-carboxamide, *N*-benzoylphenylalanyl derivative, *N*-benzoyl, and *N*-*p*-phenylbenzoyl.

Assisted Cleavage

Assisted cleavage groups include: *N*-o-nitrophenylacetyl, *N*-o-nitrophenoxyacetyl, *N*-acetoacetyl, (*N*'-dithiobenzoyloxycarbonylamino)acetyl, 10 *N*-3-(*p*-hydroxphenyl) propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutryyl, *N*-3-methyl-3-nitrobutryyl, *N*-o-nitrocinnamoyl, *N*-acetylmethionine derivative, *N*-o-nitrobenzoyl, *N*-o-(benzoyloxymethyl)benzoyl, and 4,5-diphenyl-3-oxazolin-2-one.

15 Cyclic Imide Derivatives

Cyclic imide derivatives include: *N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenyl-maleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-20 1,3,5-triazacyclohexan-2-one, and 1-substituted 3,5-dinitro-4-pyridonyl.

SPECIAL -NH PROTECTIVE GROUPS

Protective groups for – NH include: *N*-alkyl and *N*-aryl amines, imine derivatives, enamine derivatives, and *N*-hetero atom derivatives (such as *N*-metal, *N*-N, *N*-P, *N*-Si, and *N*-S), *N*-sulfonyl, and *N*-sulfonyl.

*N*-Alkyl and *N*-Aryl Amines

*N*-alkyl and *N*-aryl amines include: *N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxy]-methyl, *N*-3-acetoxypropyl, 30 *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), quaternary ammonium salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl,

*N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, and *N*-2-picolyamine *N*'-oxide.

Imine Derivatives

Imine derivatives include: *N*-1,1-dimethylthiomethylene, *N*-benzylidene,

5 *N*-*p*-methoxybenzylidene, *N*-diphenylmethylene,  
*N*-[(2-pyridyl)mesityl]methylene, *N*-(*N*',*N*'-dimethylaminomethylene),  
*N,N*'-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene,  
*N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenyl-methylene, and  
*N*-cyclohexylidene.

10 Enamine Derivative

An example of an enamine derivative is

*N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl).

*N*-Hetero Atom Derivatives

*N*-metal derivatives include: *N*-borane derivatives, *N*-diphenylborinic acid

15 derivative, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, and *N*-copper or *N*-zinc chelate. Examples of *N*-*N* derivatives include: *N*-nitro, *N*-nitroso, and *N*-oxide. Examples of *N*-P derivatives include: *N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, and *N*-diphenyl phosphoryl.

20 Examples of *N*-sulfonyl derivatives include: *N*-benzenesulfonyl, *N*-*o*-nitrobenzenesulfonyl, *N*-2,4-dinitrobenzenesulfonyl, *N*-pentachlorobenzenesulfonyl, *N*-2-nitro-4-methoxy-benzenesulfonyl, *N*-triphenylmethylsulfonyl, and *N*-3-nitropyridinesulfonyl. *N*-sulfonyl derivatives include: *N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-  
25 4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxybenzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6-tetramethyl-4-methoxybenzene- sulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy- 4-methylbenzenesulfonyl, *N*-  
30 2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl,

*N*- $\beta$ -trimethylsilylethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)-benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, and *N*-phenacylsulfonyl.

5 Disclosed compounds which are masked or protected may be prodrugs, compounds metabolized or otherwise transformed *in vivo* to yield a disclosed compound, e.g., transiently during metabolism. This transformation may be a hydrolysis or oxidation which results from contact with a bodily fluid such as blood, or the action of acids, or liver, gastrointestinal, or other enzymes.

10 Features of the invention are further described in the examples below.

## E. Examples

### BIOLOGICAL EXAMPLES

5

#### Example 1

##### **Effect of PD 198306 on streptozocin-induced static allodynia**

###### Animals

Male Sprague Dawley rats (250-300g), obtained from Bantin and Kingman, (Hull, U.K.) were housed in groups of 3. All animals were kept under a 12h light/dark cycle (lights on at 07h 00min) with food and water *ad libitum*. All experiments were carried out by an observer blind to drug treatments.

###### Development of diabetes in the rat

15 Diabetes was induced in rats by a single i.p. injection of streptozocin (50 mg/kg) as described previously (Courteix et al., 1993).

###### Evaluation of static allodynia

20 Mechanical hypersensitivity was measured using Semmes-Weinstein von Frey hairs (Stoelting, Illinois, U.S.A.). Animals were placed into wire mesh bottom cages allowing access to the underside of their paws. Animals were habituated to this environment prior to the start of the experiment. Mechanical hypersensitivity was tested by touching the plantar surface of the animals right hind paw with von Frey hairs in ascending order of force ( 0.7, 1.2, 1.5, 2, 3.6, 25 5.5, 8.5, 11.8, 15.1 and 29g) for up to 6 sec. Once a withdrawal response was established, the paw was re-tested, starting with the next descending von Frey hair until no response occurred. The highest force of 29 g lifted the paw as well as eliciting a response, thus represented the cut off point. The lowest amount of force required to elicit a response was recorded as the paw 30 withdrawal threshold (PWT) in grams.

Drugs

PD 198306 [N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide] and CI-1008 (pregabalin) were synthesized at Parke-Davis (Ann Arbor, MI, USA). PD 198306 was suspended in 5 cremophor:ethanol:water (1:1:8) vehicle. Pregabalin was dissolved in water. Both compounds were administered orally. Streptozocin (Aldrich, UK) was dissolved in 0.9% w/v NaCl and administered intraperitoneally. Drug administrations were made in a volume of 1 ml/kg.

10 Statistics

The static allodynia data were analysed using a Kruskall-Wallis ANOVA for non-parametric results, followed when significant by Mann-Whitney's t test.

Experimental protocol

15 Static allodynia was assessed with von Frey hairs, before (baseline, BL) and 1h after oral administration of PD 198306 (30mg/kg, p.o.), vehicle (cremophor:ethanol:water, 1:1:8) or pregabalin (30mg/kg, p.o.) (test). Animals were administered again the same compounds on the following day, both in the morning and the afternoon. Static allodynia was assessed only 20 before and 1h after the afternoon administration, in order to minimise the habituation of the animals to the testing conditions. Animals treated with pregabalin received water in the morning administration, in order to avoid the potential development of tolerance to the compound with repeated administration.

25

Day 1:Day 2:

a.m.: PD 198306

Water

30

Vehicle

p.m.: BL

p.m.: BL

|            |            |
|------------|------------|
| PD 198306  | PD 198306  |
| Pregabalin | Pregabalin |
| Vehicle    | Vehicle    |
| Test       | Test       |

5

## RESULTS

A single administration of pregabalin (30mg/kg, p.o.) significantly blocked streptozocin-induced static allodynia 1h after administration. In contrast, a single administration of PD 198306 (30mg/kg, p.o) had no effect on 10 streptozocin-induced static allodynia 1h after administration (see below). However, after the compound had been administered twice more on the following day, it significantly blocked streptozocin-induced static allodynia 1h after the third administration. The effects had disappeared by the following day (see FIG. 1).

15

### Example 2

## MATERIALS AND METHODS

### Animals

20 Male Sprague Dawley rats (250-300g), obtained from Charles River, Margate, U.K.) were housed in groups of 3-6. All animals were kept under a 12h light/dark cycle (lights on at 07h 00min) with food and water *ad libitum*. All experiments were carried out by an observer blind to drug treatments.

25 Diabetes was induced in rats by a single i.p. injection of streptozocin (50mg/kg) as described previously (Courteix et al., 1993).

### Development of Chronic Constriction Injury in the rat

Animals were anaesthetised with 2% isoflurane 1:4 O<sub>2</sub>/N<sub>2</sub>O mixture maintained during surgery via a nose cone. The sciatic nerve was ligated as 30 previously described by Bennett and Xie, 1988. Animals were placed on a homeothermic blanket for the duration of the procedure. After surgical preparation the common sciatic nerve was exposed at the middle of the thigh

by blunt dissection through biceps femoris. Proximal to the sciatic trifurcation, about 7mm of nerve was freed of adhering tissue and 4 ligatures (4-0 silk) were tied loosely around it with about 1mm spacing. The incision was closed in layers and the wound treated with topical antibiotics.

5

#### Intrathecal injections

PD 198306 and pregabalin were administered intrathecally in a volume of 10  $\mu$ l using a 100  $\mu$ l Hamilton syringe by exposing the spine of the rats under brief isoflurane anaesthesia. Injections were made into the intrathecal space

10 between lumbar region 5-6 with a 10 mm long 27 gauge needle. Penetrations were judged successful if there was a tail flick response. The wound was sealed with an autoclip and rats appeared fully awake within 2-3 min following injection.

#### Evaluation of static allodynia

15 Mechanical hypersensitivity was measured using Semmes-Weinstein von Frey hairs (Stoelting, Illinois, U.S.A.). Animals were placed into wire mesh bottom cages allowing access to the underside of their paws. Animals were habituated to this environment prior to the start of the experiment. Mechanical hypersensitivity was tested by touching the plantar surface of the animals right

20 hind paw with von Frey hairs in ascending order of force ( 0.7, 1.2, 1.5, 2, 3.6, 5.5, 8.5, 11.8, 15.1 and 29g) for up to 6sec. Once a withdrawal response was established, the paw was re-tested, starting with the next descending von Frey hair until no response occurred. The highest force of 29g lifted the paw as well as eliciting a response, thus represented the cut off point. The lowest

25 amount of force required to elicit a response was recorded as the paw withdrawal threshold (PWT) in grams.

#### Experimental protocol

Static allodynia was assessed with von Frey hairs, before (baseline, BL) and 0.5h, 1h and 2h after intrathecal or intraplantar administration of PD 198306 (1-30 $\mu$ g, i.t.), vehicle (cremophor:ethanol:water, 1:1:8) or pregabalin (10 $\mu$ g, i.t). For oral administration experiments, static allodynia was assessed

with von Frey hairs, before (baseline, BL) and 1h after oral administration of PD 198306 (3-30mg/kg, p.o.), vehicle (cremophor:ethanol:water, 1:1:8) or pregabalin (30mg/kg, p.o.). Animals were administered again the same compounds on the following day, both in the morning and the afternoon. Static 5 allodynia was assessed before and 1h after the morning administration. In the afternoon static allodynia was assessed before, 1h, 2h and 3h after administration for streptozocin treated animals. CCI animals were assessed before, 1h and 2h after administration

10 **Drugs used**

PD 198306 and pregabalin were synthesised at Parke-Davis (Ann Arbor, MI, USA). PD 198306 was suspended in cremophor:ethanol:water (1:1:8) vehicle. Pregabalin was dissolved in water. Both compounds were administered orally, intrathecally or intraplantar in volumes of 1ml/kg, 10 $\mu$ l and 15 100 $\mu$ l respectively. Streptozocin (Aldrich, UK) was dissolved in 0.9% w/v NaCl and administered intraperitoneally in a volume of 1ml/kg.

**Statistics**

20 Data were analysed using a Kruskall-Wallis ANOVA for non-parametric results, followed when significant by Mann-Whitney's t test vs vehicle group.

**RESULTS**

**1. Effects of PD 198306 on static allodynia, following systemic administration**

25 **1.1. Effect of PD198306 on streptozocin-induced static allodynia**

A single administration of pregabalin (30mg/kg, p.o.) significantly blocked streptozocin-induced static allodynia 1h after administration. In contrast, a single administration of PD 198306 (3-30mg/kg, p.o) had no effect on streptozocin-induced static allodynia 1h after administration (FIG. 2).

30 However, after the compound had been administered twice more on the following day, PD 198306 (30mg/kg) significantly blocked streptozocin-induced static allodynia for 2h after the third administration (FIG. 2).

**1.2. Effect of PD198306 on CCI-induced static allodynia**

A single administration of pregabalin (30mg/kg, p.o.) significantly blocked CCI-induced static allodynia 1h after administration. In contrast, neither a single or 5 multiple administration of PD 198306 (3-30mg/kg, p.o) had any effect on CCI-induced static allodynia (FIG. 3).

**2. Effects of PD 198306 on static allodynia, following intrathecal administration**

10 Intrathecally administered PD198306 (1-30 $\mu$ g) dose-dependently blocked the maintenance of static allodynia in both streptozocin (FIG. 4) and CCI animals (FIG. 5) with respective MEDs of 3 and 10  $\mu$ g. This antiallodynic effect lasted for 1h.

**15 3. Effects of PD 198306 on static allodynia, following intraplantar administration**

An intrathecal administration of PD 198306 (30 $\mu$ g) significantly blocked static allodynia in both neuropathic pain models (FIGS. 6,7). In contrast, a single administration of PD 198306 at a dose 100-fold higher (3mg/100 $\mu$ l) directly 20 into the paw had no effect on streptozocin (FIG. 6) or CCI-induced static allodynia (FIG. 7).

**REFERENCES**

25 Bennett GJ, Xie Y-K. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain* 1988;33:87-107.

Courteix C, Eschalier A and Lavarenne J. Streptozocin –induced rats: behavioural evidence for a model of chronic pain. *Pain* 1993;53:81-8

### Example 3

#### Effect of other MEK inhibitors in a neuropathic pain model in the rat

##### 5 SUMMARY

The effect of several MEK inhibitors, with different binding affinities, has been investigated in the CCI model of neuropathic pain in the rat, by assessing static allodynia with von Frey hairs. Intrathecal administration of PD219622 or PD297447 (30 $\mu$ g) had no significant effect on allodynia. This lack of effect 10 may reflect the low affinity or solubility of the compounds. However, intrathecal administration of PD 254552 or PD 184352 (30 $\mu$ g), which posses higher binding affinities, blocked the maintenance of static allodynia in CCI animals. The antiallodynic effect was only evident for 30min post-injection and thus, shorter than the one observed for pregabalin (100 $\mu$ g). The magnitude of 15 the effect was similar for 30 $\mu$ g of PD 184352 and 100 $\mu$ g of pregabalin. From this study it is concluded that MEK inhibitors exert an antiallodynic effect in CCI-induced neuropathic rats when administered intrathecally, and that the antiallodynic effect correlates with the affinity of the compounds.

20 The animals and methods for developing chronic constriction injury in the rat, injecting test compounds, and evaluation of static allodynia were according to Example 2 above. PD219622, PD297447, PD 184352, PD 254552 and pregabalin were administered intrathecally at doses of 30 $\mu$ g for all PD compounds and 100 $\mu$ g for pregabalin. Static allodynia was assessed with 25 von Frey hairs, before (baseline, BL) and 0.5h, 1h and 2h after intrathecal administration of the compounds

##### Drugs used

PD297447, PD219622, PD 254552, PD 184352 (CI-1040), and pregabalin 30 were synthesised at Parke-Davis (Ann Arbor, MI, USA). PD297447, PD219622, PD 254552 and PD 184352 were suspended in

cremophor:ethanol:water (1:1:8) vehicle. Pregabalin was dissolved in water. All compounds were administered intrathecally in a 10 $\mu$ l volume.

#### Statistics

5 Data were analysed using a Kruskall-Wallis ANOVA for non-parametric results, followed when significant by Mann-Whitney's t test vs vehicle group.

#### RESULTS

Intrathecally administered PD297447 or PD219622 (30 $\mu$ g) had no 10 significant effect on allodynia. This lack of effect may reflect the low affinity of the compounds (965nM and 100nM respectively). However, intrathecal administration of PD 184352 or PD 254552 (30 $\mu$ g) blocked the maintenance 15 of static allodynia in CCI animals (see FIG. 8). These compounds possess higher affinity (2 and 5 nM respectively). The antiallodynic effect was only evident for 30min post-injection and thus, shorter than the one observed for pregabalin (100 $\mu$ g). The magnitude of the effect was similar for 30 $\mu$ g of PD 184352 and 100 $\mu$ g of pregabalin.

The results indicate that MEK inhibitors exert an antiallodynic effect in 20 CCI-induced neuropathic rats when administered intrathecally, and that the antiallodynic effect correlates with the affinity of the compounds.

CHEMICAL EXAMPLES

## EXAMPLE 1

5 [4-Chloro-2-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-phenyl]-[4-iodo-2-methyl-phenyl]-amine (18). (Scheme 2, R<sub>1</sub>=Cl, R<sub>2</sub>=R<sub>3</sub>=H, R<sub>4</sub>=CH<sub>3</sub>)

a). A mixture of 5-chloro-2-methoxybenzoic acid 16 (14.8 g, 0.0793 mole) and SOCl<sub>2</sub> (28.31 g, 14.97 ml, 0.1584 mole) was refluxed for 2 hours and excess SOCl<sub>2</sub> removed leaving a white residue. The solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and added to a solution of 2-amino-2-methyl-1-propanol (13.98 g, 14.97 ml, 0.1584 mole) in CH<sub>2</sub>Cl<sub>2</sub> cooled with ice-bath. The ice-bath was removed, and after stirring at room temperature for 3 hours a white solid precipitated. The precipitate was separated by filtration and discarded. The filtrate was concentrated leaving a thick colorless oil. SOCl<sub>2</sub> (17.4 ml) was added to the oil dropwise. An exothermic reaction took place resulting in to a freely flowing solution. After stirring for 30 minutes, the reaction mixture was poured in to Et<sub>2</sub>O (200 ml). An oil separated out. The Et<sub>2</sub>O layer was removed by decanting and discarded. The oily residue was dissolved in a minimum amount of water, basified with aqueous 20% NaOH, and extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O layer was dried (K<sub>2</sub>CO<sub>3</sub>) and concentrated to give 17 as tan oil. Yield 14.63 g (77%).

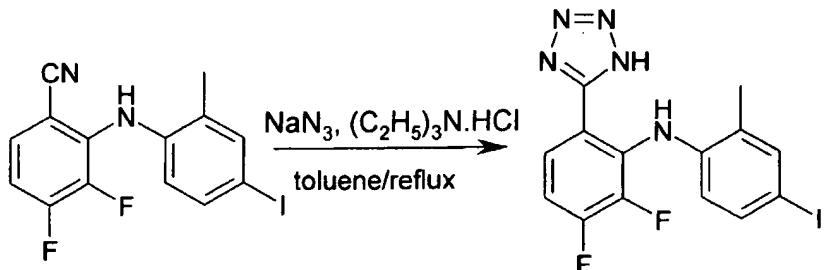
b). LDA (5 ml of 2.0 M solution in THF) was added to a solution of 4-iodo-2-methylaniline (2.33 g, 0.010 mole) in THF (15 ml) at -78 °C. The mixture was stirred at -78 °C for 30 minutes. To this, a solution of 17 (1.199 g, 0.005 mole) in THF (15 ml) was added. The mixture stirred for 16 hours as it warmed up to room temperature. The reaction mixture was quenched with aqueous NH<sub>4</sub>Cl and extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O layer was dried (MgSO<sub>4</sub>) and concentrated to give crude 18 as brown oil. The oil was purified on silica column chromatography. Eluting with CH<sub>2</sub>Cl<sub>2</sub> gave pure 1.7 g (77%) of 18 as brown oil. Four hundred and nine milligrams of the oil were dissolved in Et<sub>2</sub>O and treated with Et<sub>2</sub>O-HCl giving the HCl salt as a light yellow solid

precipitate. Yield 356.4 mg (81%); mp 324-330 °C; Anal. Calcd/found for  $C_{18}H_{18}N_2OCl\bullet HCl \cdot 0.5H_2O$ : C, 44.47/44.32; H, 4.15/3.94; N, 5.76/5.66.

## EXAMPLE 2

5

### [2,3-Difluoro-6-(1*H*-tetrazol-5-yl)-phenyl]- (4-iodo-2-methyl-phenyl)-amine



10 [2,3-Difluoro-6-cyano-phenyl]- (4-iodo-2-methyl-phenyl)-amine (1.11g, 3mmol) and Sodium azide(0.255g, 3.9mmol) and triethylamine hydrochloride (0.537g, 3.9mmol) were all suspended in 10ml toluene and stirred at 100°C for 12 hours. The mixture was concentrated and the residue purified by column chromatography with ethyl acetate/methanol (10/1) to give the product 15 as a foam-like solid. The yield: ~50%

m.p: 83.4-88.7°C

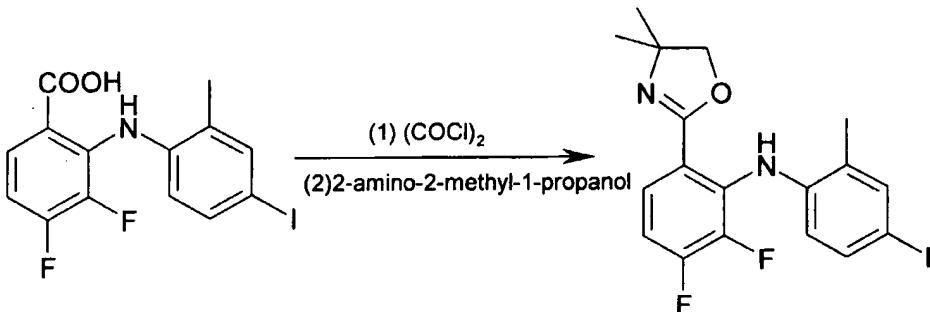
$^1H$  NMR(CDCl<sub>3</sub>, 400Hz):  $\delta$ /ppm 7.69(1H, m, Phenyl-H); 7.42(1H, s, Phenyl-H); 7.27(1H, m, Phenyl-H); 6.91(1H, dd, J=16.2Hz, 8.3Hz, Phenyl-H); 6.40(1H, dd, Phenyl-H); 2.28(3H, s, CH<sub>3</sub>)

20

## EXAMPLE 3

[6-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]- (4-iodo-2-methyl-phenyl)-amine

5



10

A solution of 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (1.17g, 3mmol), oxalyl chloride (0.457g, 3.6mmol) in 30ml dichloromethane was treated with 2 drops of dimethylformamide, stirred at room temperature for 3 hours then concentrated. The residue was dissolved in 25 ml dichloromethane then the solution was added dropwise to a solution of 2 amino-2-methyl-1-propanol (0.623g, 7mmol) in 25 ml dichloromethane at 0°C, then stirred at room temperature for 12 hours, filtered off the precipitate, the filtration was washed with water, 5% aqueous sodium bicarbonate, 1 N HCl, brine, dried with sodium sulfate. Concentration gave the crude product, then resuspended in 25 ml chloroform, then thionyl chloride was added at 0°C and stirred at room temperature for 15 hours, then concentrated and the residue was dissolved in 30 ml dichloromethane, 1 N HCl was added to adjusted the pH value to 11, the separated and extracted with chloroform, dried with sodium sulfate. Concentrated and then run column with hexanes/dichloromethane (20/1) to give the compound as a white crystal.

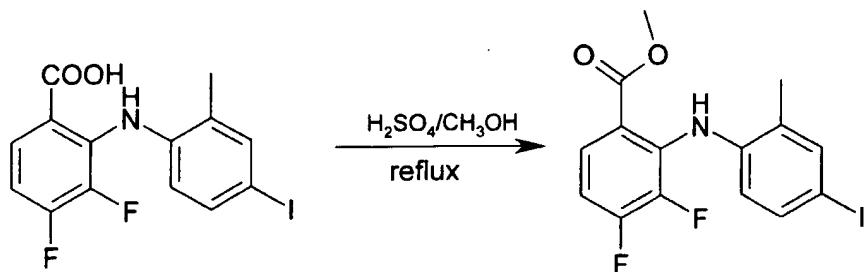
15

The yield: 65%

m.p.: 103.7-104.4°C

<sup>1</sup>H NMR(CDCl<sub>3</sub>, 400Hz): δ/ppm 10.2(1H, s, NH), 7.48-7.58(1H, m, Phenyl-H); 7.48(1H, s, Phenyl-H); 7.38(1H, d, J=8.5Hz, Phenyl-H), 6.66-6.72(1H, m, Phenyl-H); 6.58(1H, t, J=8.0Hz, Phenyl-H); 4.01(2H, s, -CH<sub>2</sub>-); 2.31(3H, s, Phenyl-CH<sub>3</sub>); 1.32(6H, s, -C(CH<sub>3</sub>)<sub>2</sub>-)

## EXAMPLE 4

5 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid methyl ester

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (5g) was dissolved  
 10 in 100ml methanol and 5 drops of concentrated sulfuric acid was added, reflux  
 for 4 days. Run column with hexanes/dichloromethane to give the product as  
 a white solid, yield: 50%.

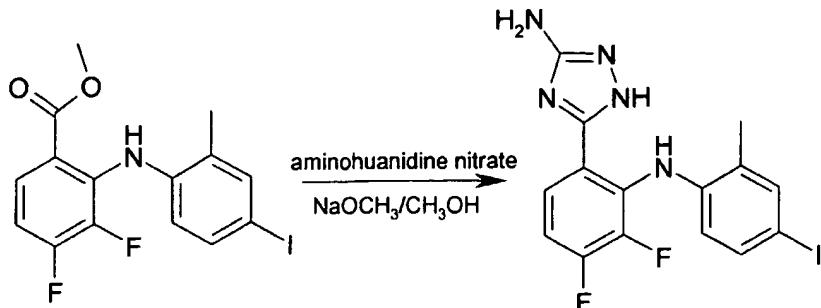
m.p.:90.1-90.4°C

<sup>1</sup>H NMR(CDCl<sub>3</sub>, 400Hz): δ/ppm 8.92(1H, s, NH), 7.75-7.78(1H, m, Phenyl-H);  
 15 7.49(1H, s, Phenyl-H); 7.38(1H, dd, J=8.5Hz, 2.0Hz, Phenyl-H), 6.66-6.73(1H,  
 m, Phenyl-H); 6.56-6.60(1H, m, Phenyl-H); 3.88(3H, s, -OCH<sub>3</sub>); 2.30(3H, s,  
 Phenyl-CH<sub>3</sub>)

## EXAMPLE 5

5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4*H*-[1,2,4]triazol-3-ylamine

5

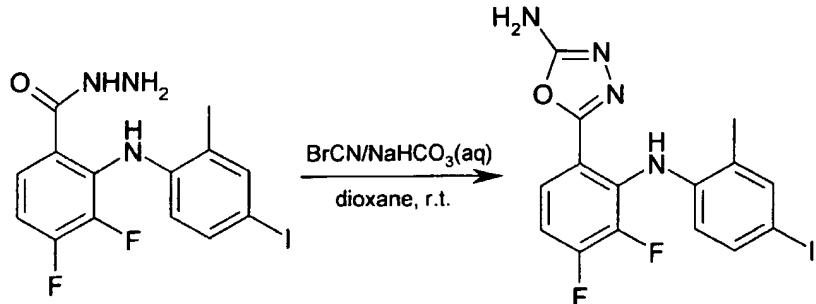


10 Aminoguanidine nitrate (1.65g, 12mmol) was added to a solution of sodium methoxide (0.648g, 12mmol) in methanol (12ml) at 0°C, then 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid methyl ester was added as a solution of methanol and reflux for 20 hours, concentration and run column with hexanes/ethyl acetate to give the product as a white crystal. The yield: 60%  
 m.p.: 191.7-192.0°C  
 15  $^1\text{H}$  NMR(DMSO, 400Hz):  $\delta$ /ppm 9.45(1H, s, -NH-); 7.79(1H, t,  $J$ =7.3Hz, Phenyl-H); 7.51(1H, s, Phenyl-H); 7.35(1H, d,  $J$ =10.1Hz, Phenyl-H); 7.05-7.11(1H, m, Phenyl-H); 6.44-6.48(1H, m, Phenyl-H); 6.32(2H, s, -NH<sub>2</sub>), 2.32(3H, s, CH<sub>3</sub>)

## EXAMPLE 6

5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine

5



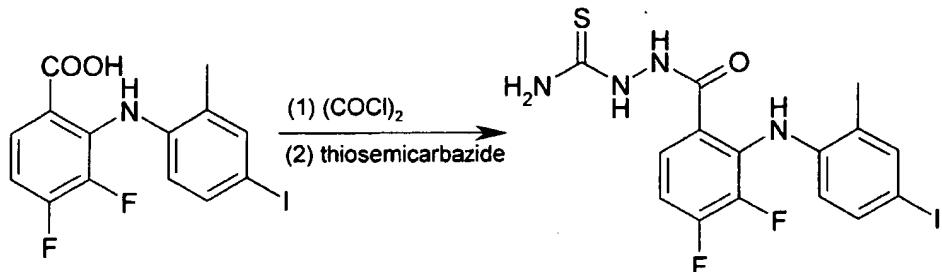
To a solution of 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid hydrazide (0.806g, 2mmol) in 5ml of dioxane was added cyanogen bromide (0.212g, 2mmol) followed by a solution of sodium bicarbonate (0.17g, 2mmol) 10 in 5ml of water. The resulting mixture was stirred 18 hours at room temperature the solution was concentrated and the residue was run column with hexanes/ethyl acetate (3/1) to give the product which was recrystallized from ethyl acetate / hexanes to provide a pale-yellow crystal. The yield: 58% m.p.: 183.7-184.0°C

15  $^1\text{H}$  NMR( $\text{CDCl}_3$ , 400Hz):  $\delta$ /ppm 8.87(1H, s, -NH-); 7.52(1H, s, Phenyl-H); 7.45-7.49(1H, m, Phenyl-H); 7.40(1H, d,  $J=8.3\text{Hz}$ , Phenyl-H); 6.77-6.83(1H, m, Phenyl-H); 6.60-6.63(1H, m, Phenyl-H); 5.02(2H, s, -NH<sub>2</sub>), 2.36(3H, s, CH<sub>3</sub>)

## EXAMPLE 7

2-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoyl]hydrazinecarbothioamide

5



A solution of 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (3.9g, 0.01mol), oxalyl chloride (1.90g, 0.015mol) in 40ml dichloromethane was treated with 2 drops of dimethylformamide, stirred at room temperature for 3 hours before concentration. The residue was dissolved in 10 ml tetrahydrofuran and added to a solution of thiosemicarbazide (2.0g, 0.022mol) in 50ml tetrahydrofuran at 0°C, stirred at room temperature for 14 hours. Concentrated and run column chromatography with hexanes/ethyl acetate (1/1) to give the product as a yellow solid. 2.91g. The yield: 63%

10 m.p.: 159.5-160.0°C

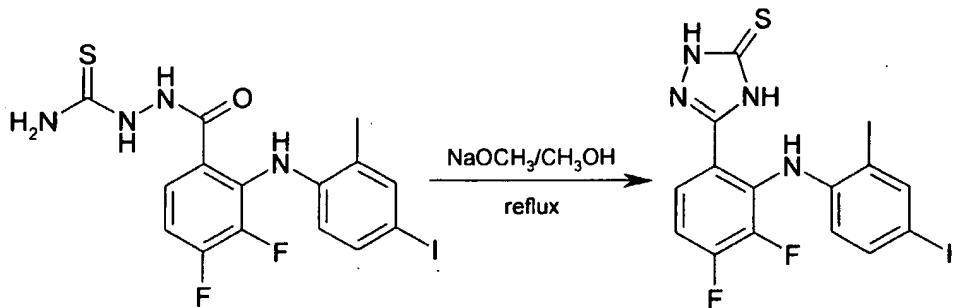
<sup>1</sup>H NMR(DMSO, 400Hz): δ/ppm 10.58(1H, s, -NH-); 9.28(1H, s, -NH-); 8.83(1H, s, -NH-); 7.95(1H, s, Phenyl-H); 7.12-7.75(2H, m, NH<sub>2</sub>); 7.51(1H, s, Phenyl-H); 7.37(1H, dd, J=8.6Hz, 1.7Hz, Phenyl-H); 7.16(1H, dd, J=17Hz, 9.0Hz, Phenyl-H); 6.40-6.50(1H, m, Phenyl-H); 5.02(2H, s, -NH<sub>2</sub>), 2.00(3H, s,

15 CH<sub>3</sub>)

## EXAMPLE 8

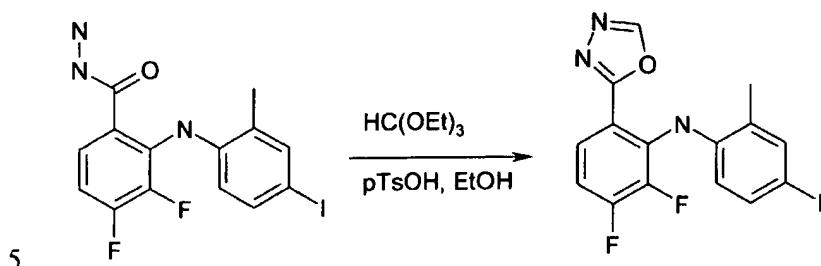
5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol

5



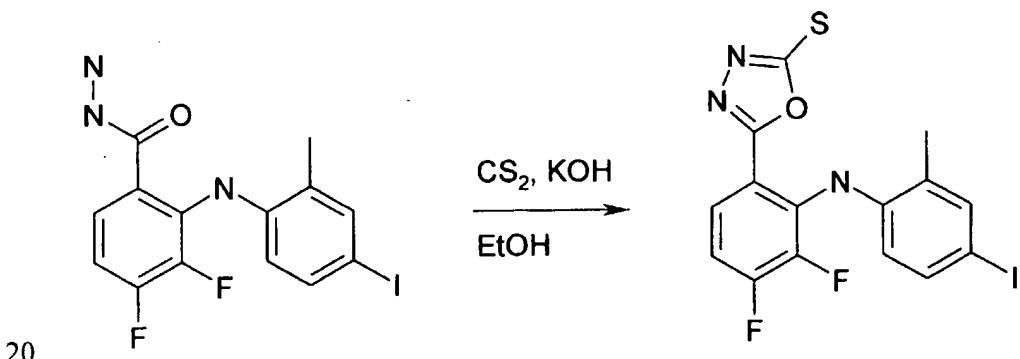
2-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-  
benzoyl]hydrazinecarbothioamide (1.386g, 3mmol) was dissolved in 15 ml  
10 anhydrous methanol, sodium methoxide (25% wt% in methanol) 2.5ml was  
added at 0°C in one portion. The resulting mixture was heated at reflux for 17  
hours before concentration. Run column with hexanes/ethyl acetate to give  
the product as a needle white crystal. The yield: 40%  
m.p.: 196.5(dec.)  
15 <sup>1</sup>H NMR(DMSO, 400Hz): δ/ppm 13.87(1H, s, -NH-); 13.80(1H, s, -NH-);  
8.16(1H, s, -NH-); 7.61-7.65(1H, m, Phenyl-H); 7.48(1H, s, Phenyl-H);  
7.32(1H, dd, J=8.6Hz, 2.2Hz, Phenyl-H); 7.24(1H, dd, J=16.4Hz, 9.5Hz,  
Phenyl-H); 6.42-6.46(1H, m, Phenyl-H); 5.02(2H, s, -NH<sub>2</sub>), 2.20(3H, s, CH<sub>3</sub>).

## EXAMPLE 9

(2,3-Difluoro-6-[1,3,4]oxadiazol-2-yl-phenyl)-(4-iodo-2-methyl-phenyl)-amine

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid hydrazide (146 mg, 0.36 mmol) was suspended in 7 mL of absolute EtOH and 2 mL of  $\text{HC(OEt)}_3$  was added along with approximately 3 mg of  $\text{pTsOH}$ . The reaction 10 was heated to reflux for 3h, cooled and concentration on a rotary evaporator. The reaction was purified ( $\text{SiO}_2$ , 4:1 Hexane/EtOAc) to afford 117 mg (79%) of (2,3-difluoro-6-[1,3,4]oxadiazol-2-yl-phenyl)-(4-iodo-2-methyl-phenyl)-amine as a yellow powder. M.p. = 144.4 – 145.5 °C.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.89 (s, 1H), 8.44 (s, 1H), 7.66 (m, 1H), 7.52 (d,  $J$  = 1.7 Hz, 1 H), 7.38 (dd,  $J$  = 15 8.5, 1.9 Hz, 1 H), 6.83 (m, 1H), 6.14 (dd,  $J$  = 8.5, 5.9 Hz, 1 H), 2.37 (s, 3 H).

## EXAMPLE 10

5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid hydrazide (170 mg, 0.42 mmol) was suspended in 7 mL of absolute EtOH and cooled to

0 °C. Carbon disulfide (74 mg, 0.97 mmol) was added followed by 24 mg (0.42 mmol) of powdered KOH. The reaction was stirred for 1 h at 0 °C, 1h at rt, and refluxed for 3 h to afford a homogeneous reaction. The reaction was cooled to rt, at which point a ppt formed. Water was added and the reaction 5 diluted with 5 mL of EtOAc. 1N HCl was added to acidify the aqueous layer (pH = 2). The aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to obtain 96 mg (51%) of 5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol as a yellow powder. M.p. = 231.8 – 232.8 °C. <sup>1</sup>H 10 NMR (400MHz, CDCl<sub>3</sub>) δ 7.62 (m, 2H), 7.47 (s, 1H), 7.30 (complex m, 2H), 6.44 (dd, J = 8.0, 4.5 Hz, 1H), 2.19 (s, 3H).

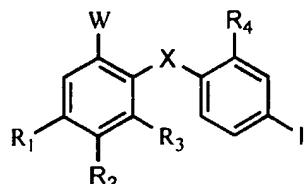
#### F. OTHER EMBODIMENTS

From the above disclosure and examples, and from the claims below, the essential features of the invention are readily apparent. The scope of the 15 invention also encompasses various modifications and adaptations within the knowledge of a person of ordinary skill. Examples include a disclosed compound modified by addition or removal of a protecting group, or an ester, pharmaceutical salt, hydrate, acid, or amide of a disclosed compound. Publications cited herein are hereby incorporated by reference in their 20 entirety.

What is claimed is:

CLAIMS

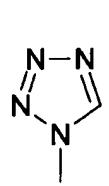
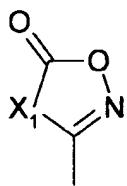
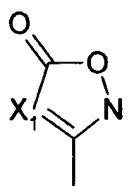
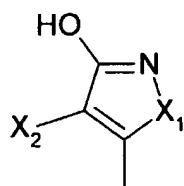
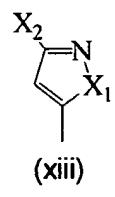
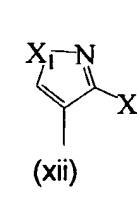
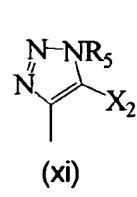
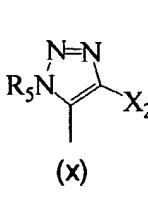
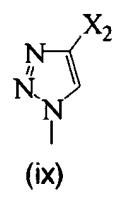
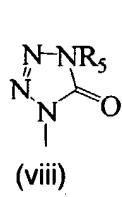
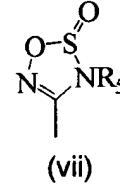
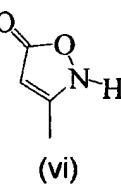
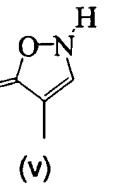
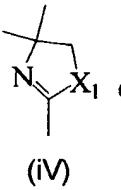
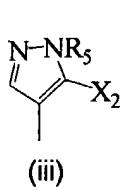
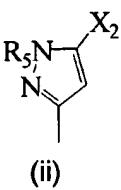
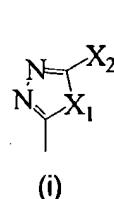
1. A method for treating chronic pain, said method comprising  
 administering to a subject in need of such treatment a composition comprising  
 5 a MEK inhibitor selected from: a compound of formula (I):



(I)

10

W is one of the following formulae (i) – (xiii):



15

X1 is O, S, or NR5;

X<sub>2</sub> is OH, SH, or NHR<sub>E</sub>;

each of R<sub>E</sub> and R<sub>F</sub> is H or C<sub>1-4</sub> alkyl;

5

each of R<sub>1</sub> and R<sub>2</sub> is independently selected from H, F, NO<sub>2</sub>, Br and Cl; R<sub>1</sub> can also be SO<sub>2</sub>NR<sub>G</sub>R<sub>H</sub>, or R<sub>1</sub> and R<sub>2</sub> together with the benzene ring to which they are attached constitute an indole, isoindole, benzofuran, benzothiophene, indazole, benzimidazole, or benzthioazole;

10

R<sub>3</sub> is H or F;

each of R<sub>G</sub>, R<sub>H</sub>, and R<sub>4</sub> is independently selected from H, Cl and CH<sub>3</sub>;

15

R<sub>5</sub> is H or C<sub>3-4</sub> alkyl; and

wherein each hydrocarbon radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, hydroxyl, amino, (amino)sulfonyl, and NO<sub>2</sub>; and

20

wherein each heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>3-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, phenyl, hydroxyl, amino, (amino)sulfonyl, and NO<sub>2</sub>, wherein each substituent alkyl, cycloalkyl, alkenyl,

25

alkynyl or phenyl is in turn optionally substituted with between 1 and 2 substituents independently selected from halo, C<sub>1-2</sub> alkyl, hydroxyl, amino, and NO<sub>2</sub>;

or a pharmaceutically acceptable salt or C<sub>1-8</sub> ester thereof.

30

2. The method of claim 1, wherein said chronic pain is selected from neuropathic pain, idiopathic pain, and pain associated with chronic alcoholism, vitamin deficiency, uremia, or hypothyroidism.
3. The method of claim 2, wherein said chronic pain is a type of neuropathic pain.
4. The method of claim 3, wherein said neuropathic pain is associated with one of the following: inflammation, postoperative pain, phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma, vasculitis, viral infection, crush injury, constriction injury, tissue injury, limb amputation, post-operative pain, arthritis pain, and any other nerve injury between the peripheral nervous system and the central nervous system, inclusively.
5. The method of claim 2, wherein said chronic pain is associated with chronic alcoholism, vitamin deficiency, uremia, or hypothyroidism.
6. The method of claim 2, wherein said chronic pain is associated with idiopathic pain.
- 20 7. The method of claim 1, wherein said chronic pain is associated with inflammation.
8. The method of claim 1, wherein said chronic pain is associated with arthritis.
- 25 9. The method of claim 1, wherein said chronic pain is associated with post-operative pain.
- 30 10. The method of claim 1, wherein R<sub>1</sub> is bromo or chloro.

11. A method of claim 1, wherein  $R_2$  is fluoro.
12. A method of claim 1, wherein  $R_3$  is H.  
5
13. A method of claim 12, wherein each of  $R_2$  and  $R_3$  is H.
14. A method of claim 1, wherein each of  $R_2$  and  $R_3$  is fluoro.
- 10 15. A method of claim 14, wherein  $R_1$  is bromo.
16. A method of claim 14, wherein  $R_1$  is fluoro.
17. A method of claim 1, wherein  $R_2$  is nitro.  
15
18. A method of claim 16, wherein  $R_3$  is H.
19. A method of claim 1, wherein  $R_4$  is chloro.
- 20 20. A method of claim 1, wherein  $R_4$  is methyl.
21. A method of claim 1, wherein  $R_5$  is H.
22. A method of claim 1, wherein  $R_5$  is  $CH_3$ .  
25
23. A method of claim 1, wherein  $X_1$  is O or S.
24. A method of claim 1, wherein  $X_1$  is NH or  $NCH_3$ .
- 30 25. A method of claim 1, wherein  $X_2$  is OH, SH, or  $NH_2$ .
26. A method of claim 1, wherein  $X_2$  is  $NHCH_3$  or OH.

27. A method of claim 1, wherein said MEK inhibitor has a structure selected from: [5-fluoro-2-(1H-tetrazol-5-yl)-phenyl]-[4-iodo-2-methyl-phenyl]-amine; [2,3-difluoro-6-(1H-tetrazol-5-yl)-phenyl]-[4-iodo-2-methyl-phenyl]-amine; (4-iodo-2-methyl-phenyl)-[2,3,4-trifluoro-6-(1H-tetrazol-5-yl)-phenyl]-amine; [4-bromo-2,3-difluoro-6-(1H-tetrazol-5-yl)-phenyl]-[4-iodo-2-methyl-phenyl]-amine; [5-fluoro-4-nitro-2-(1H-tetrazol-5-yl)-phenyl]-[4-iodo-2-methyl-phenyl]-amine; [2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-5-fluoro-phenyl]-[4-iodo-2-methyl-phenyl]-amine; [6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-[4-iodo-2-methyl-phenyl]-amine; [6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3,4-trifluoro-phenyl]-[4-iodo-2-methyl-phenyl]-amine; [4-bromo-6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-[4-iodo-2-methyl-phenyl]-amine; [2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-5-fluoro-4-nitro-phenyl]-[4-iodo-2-methyl-phenyl]-amine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; and 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ol.



trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; and 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazole-3-thiol.

5

29. A method of claim 1, wherein said MEK inhibitor has a structure selected from: 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isothiazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isoxazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1H-pyrazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isothiazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol.

methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 1-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; and 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1-methyl-1H-pyrazol-3-ol.

1H-[1,2,3]triazol-4-ol; 1-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; and 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1H-[1,2,3]triazol-4-ol.

31. The method of claim 1, wherein said MEK inhibitor has a structure selected from: 3-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-2H-isoxazol-5-one; [5-fluoro-2-(2-oxo-2,3-dihydro-2l>4-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]- (4-iodo-2-methyl-phenyl)-amine; [2,3-difluoro-6-(2-oxo-2,3-dihydro-2l>4-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]- (4-iodo-2-methyl-phenyl)-amine; (4-iodo-2-methyl-phenyl)-[2,3,4-trifluoro-6-(2-oxo-2,3-dihydro-2l>4-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-amine; [4-bromo-2,3-difluoro-6-(2-oxo-2,3-dihydro-2l>4-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]- (4-iodo-2-methyl-phenyl)-amine; [5-fluoro-4-nitro-2-(2-oxo-2,3-dihydro-2l>4-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]- (4-iodo-2-methyl-phenyl)-amine; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; and 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-isoxazol-5-one.

32. The method of claim 1, wherein said MEK inhibitor has a structure selected from: 2,4-bis-(2-chloro-4-iodo-phenylamino)-3fluoro5-nitro-benzoic acid; 5-[3,4difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; (2,3-difluoro-6-[1,3,4]oxadiazol-2-yl-phenyl)(-(4-iodo-2-

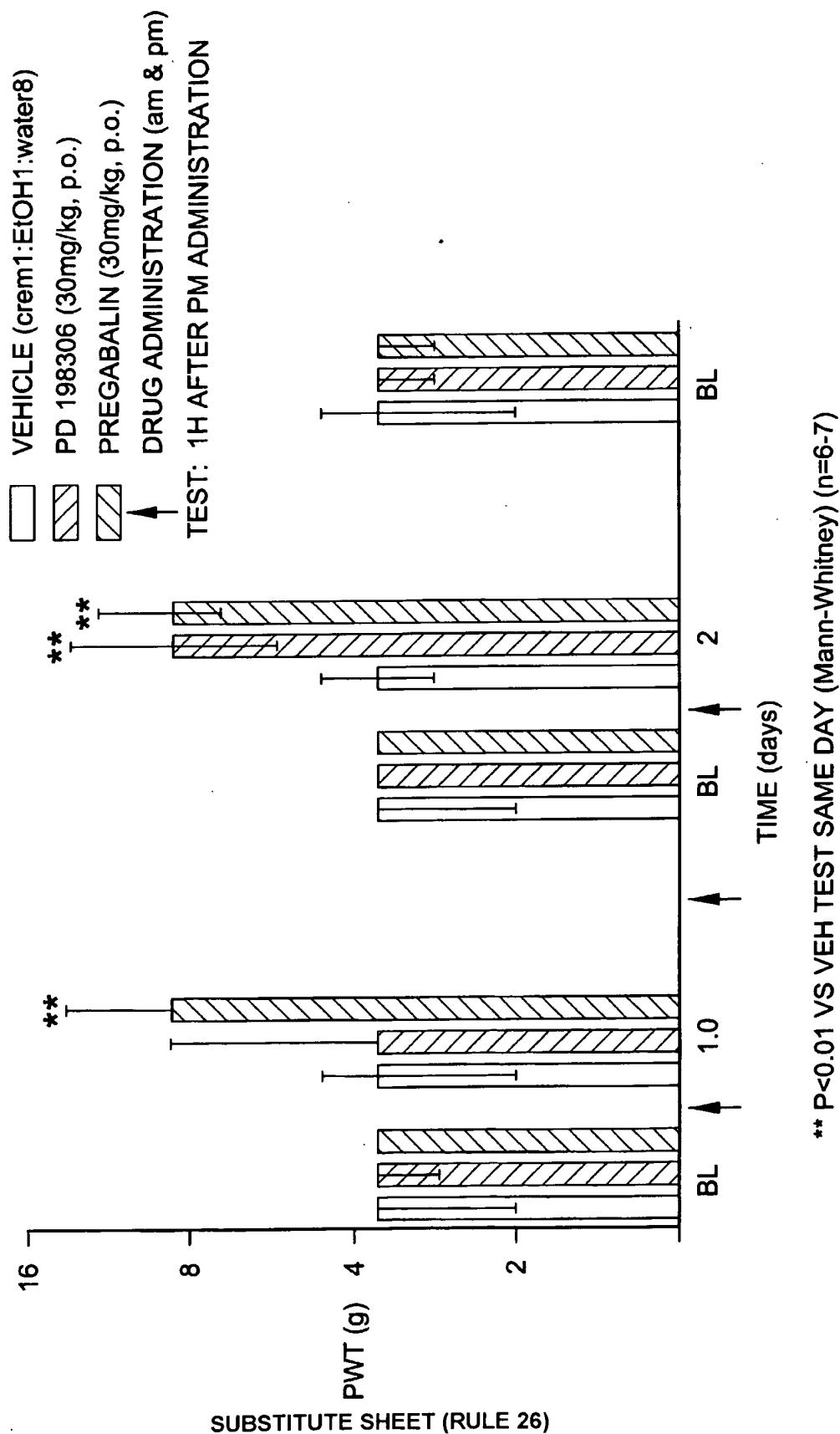
methyl-phenyl)-amine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4*H*-[1,2,4]triazole-3-ylamine; and 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4*H*-[1,2,4]triazole-3-thiol.

5

33. The method of claim 1, wherein said MEK inhibitor has the structure: 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid.

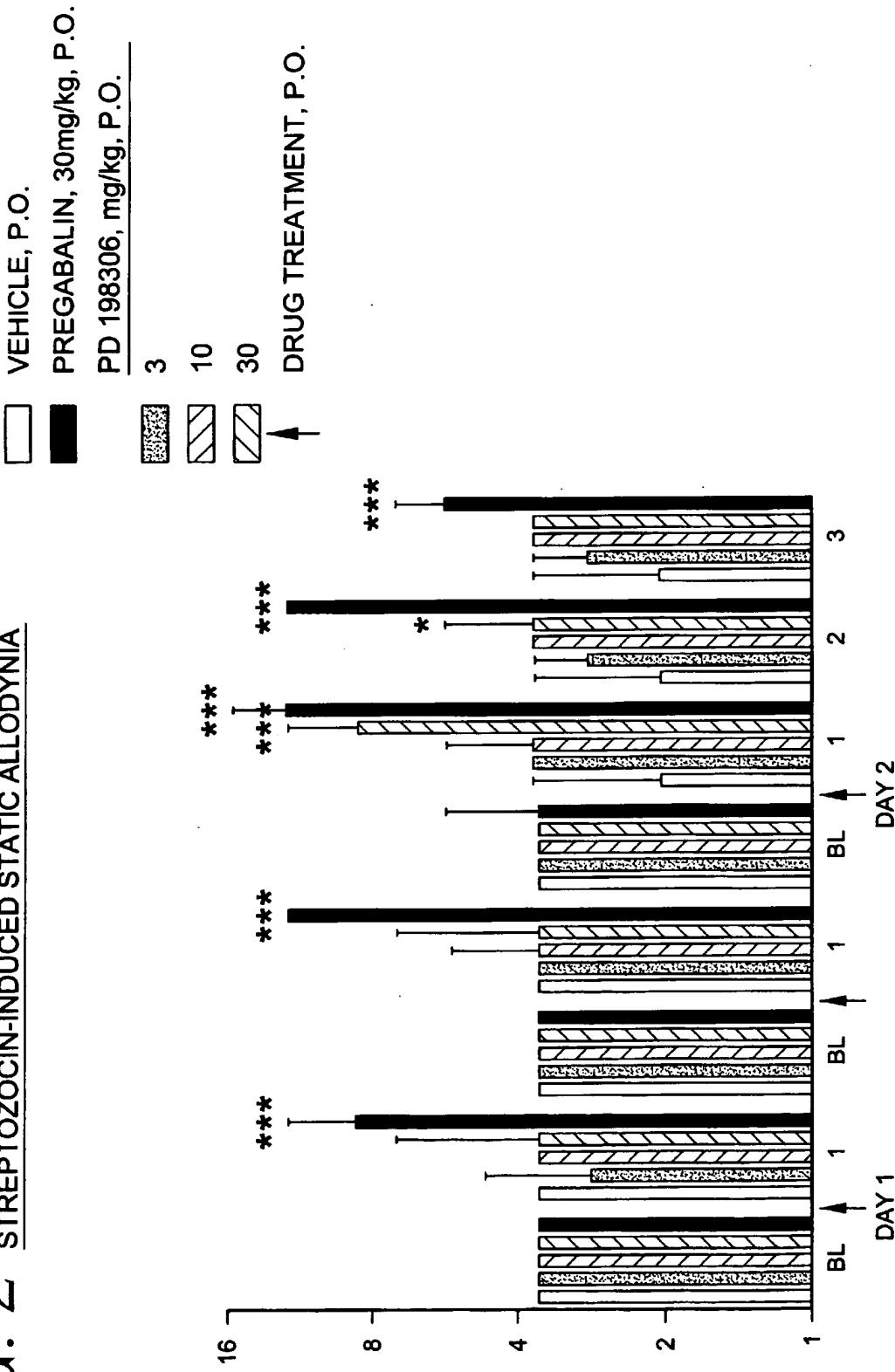
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**FIG. 1** EFFECT OF PD 198306 ON STREPTOZOCIN-INDUCED STATIC ALLODYNIA



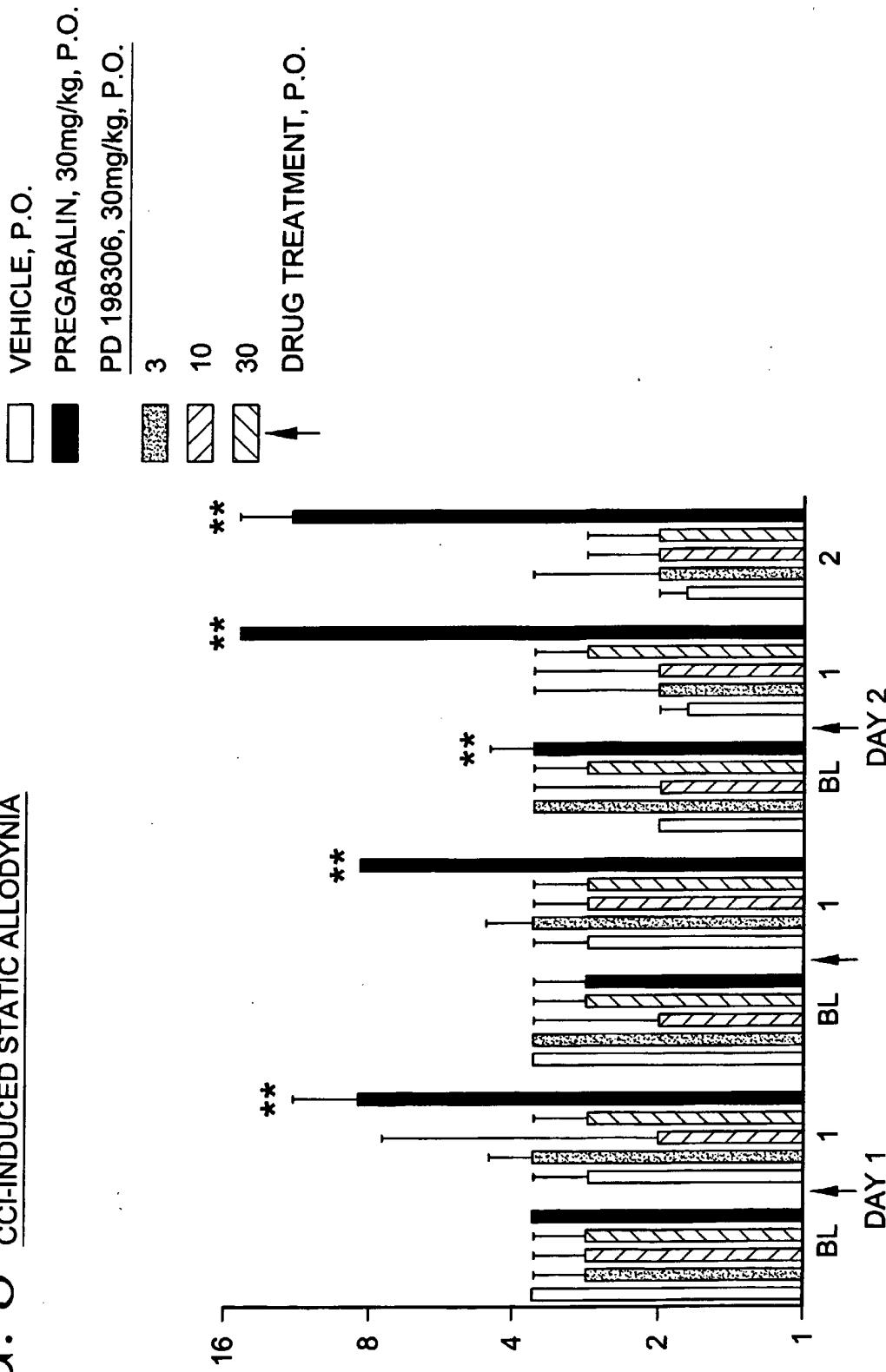
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**FIG. 2** EFFECT OF SYSTEMIC (p.o.) ADMINISTRATION OF PD 198306 ON STREPTOZOCIN-INDUCED STATIC ALLODYNIA



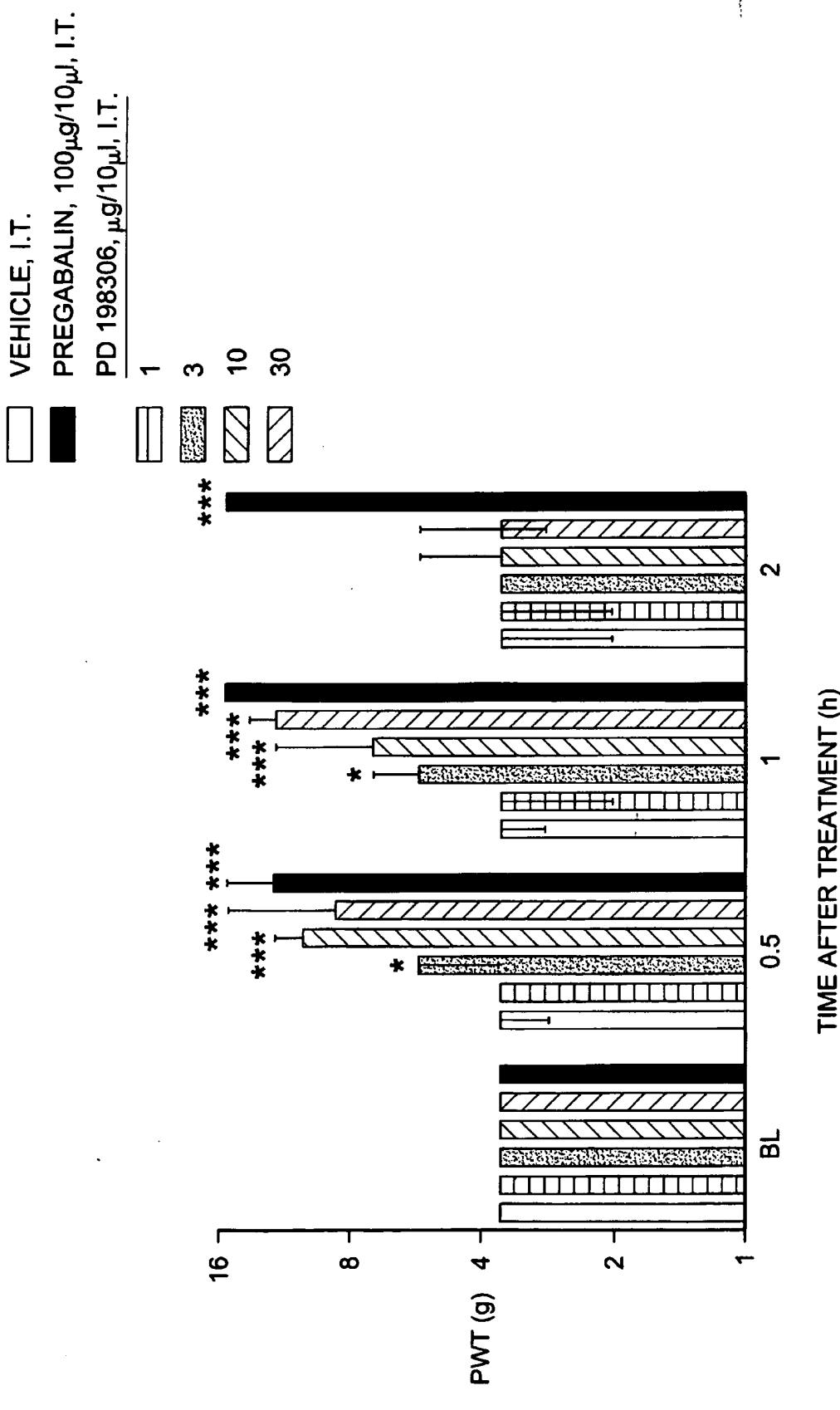
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**FIG. 3**  
**EFFECT OF SYSTEMIC (p.o.) ADMINISTRATION OF PD 198306 ON**  
**CCI-INDUCED STATIC ALLODYNIA**



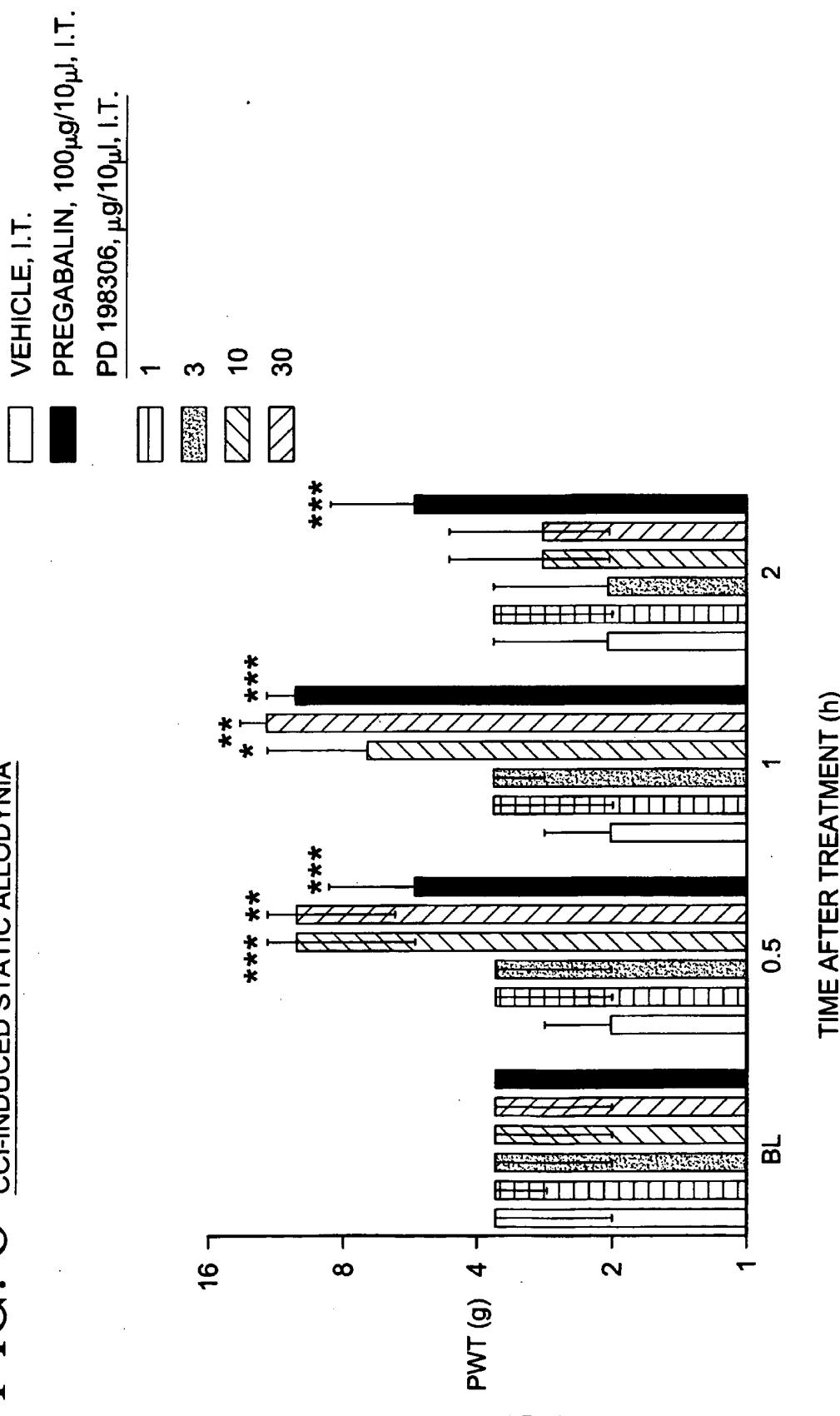
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**FIG. 4**  
EFFECT OF INTRATHECAL (i.t.) ADMINISTRATION OF PD 198306 ON  
 STREPTOZOCIN-INDUCED STATIC ALLODYNIA



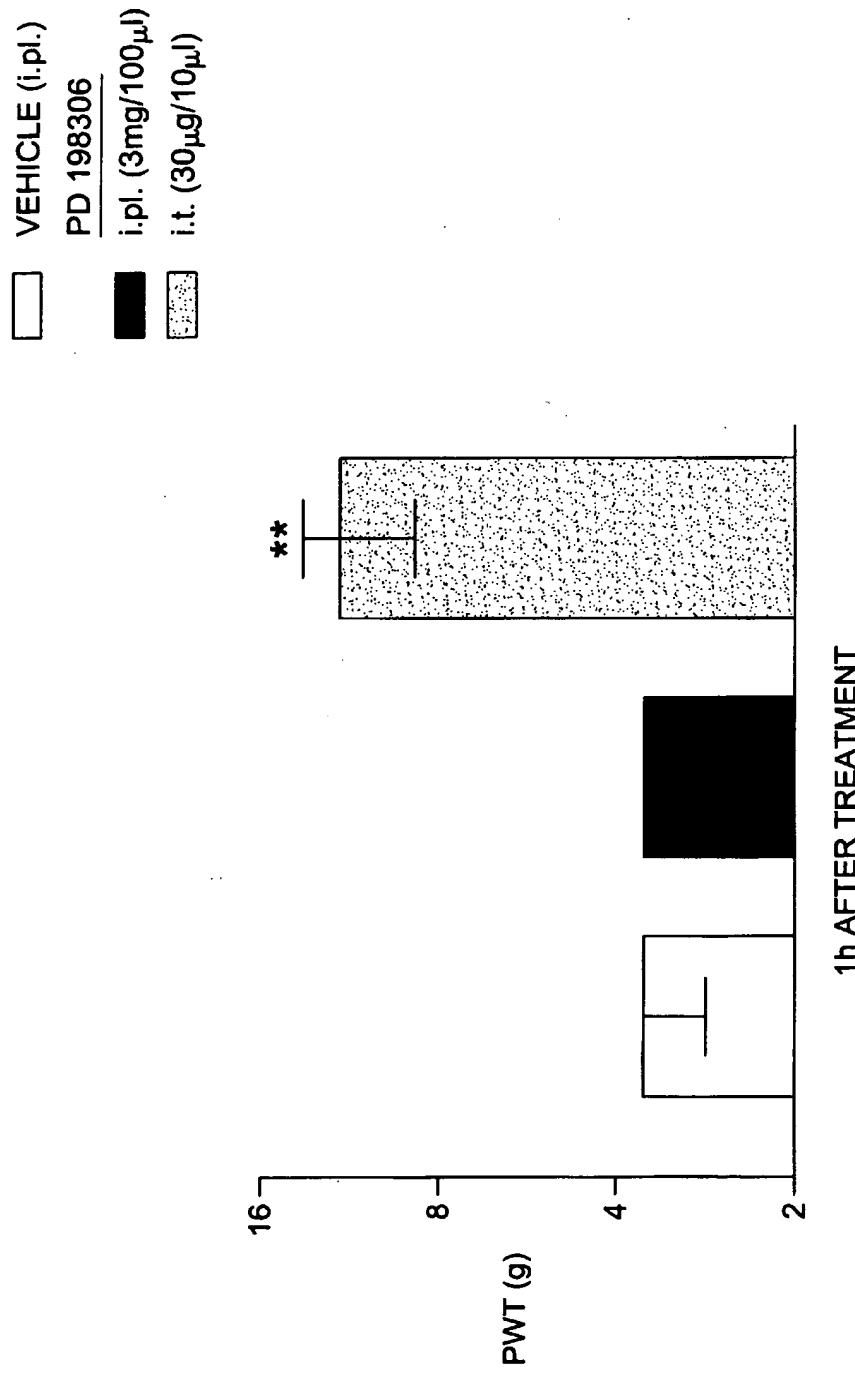
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**FIG. 5**  
EFFECT OF INTRATHECAL (i.t.) ADMINISTRATION OF PD 198306 ON  
CCI-INDUCED STATIC ALLODYNIA



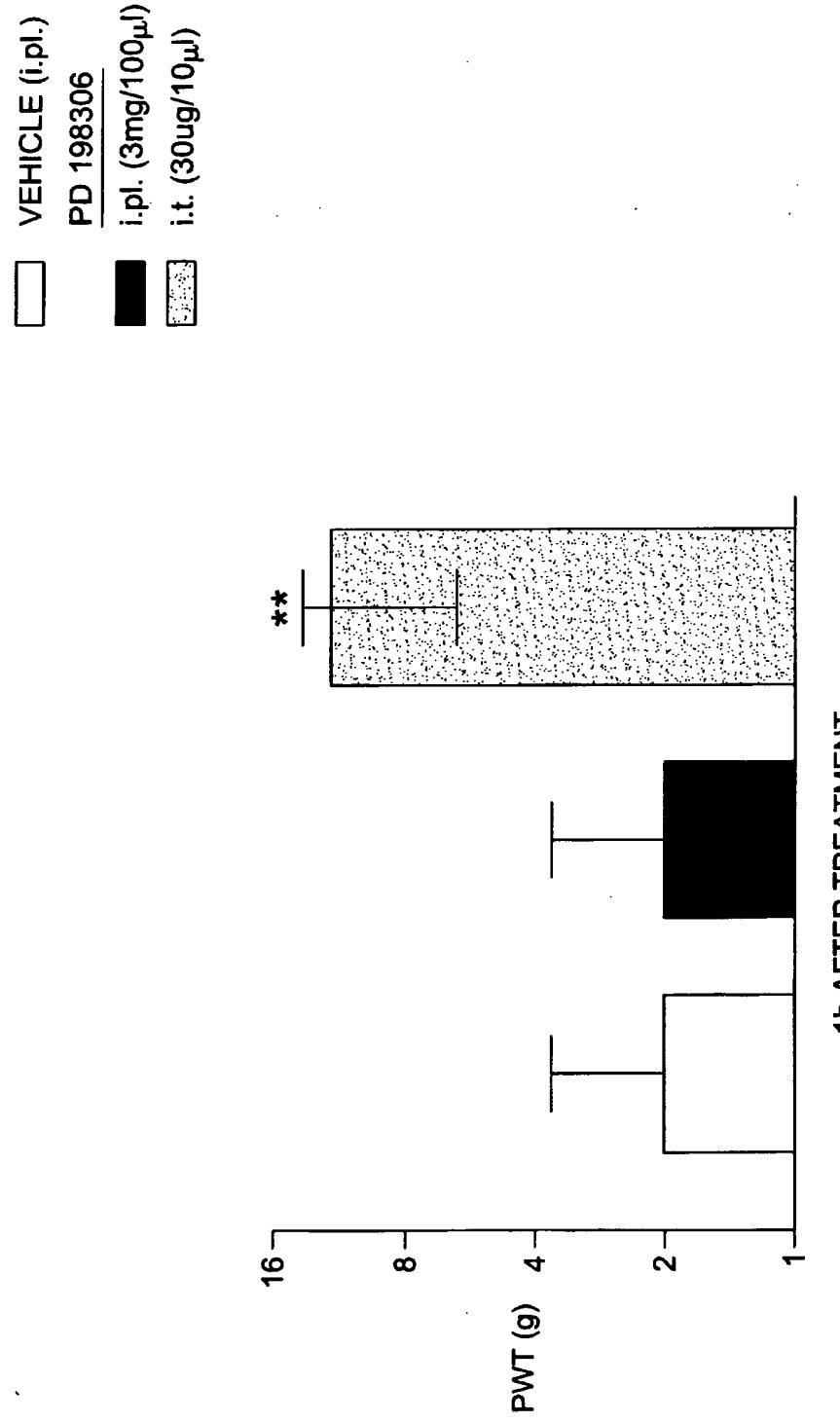
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FIG. 6 EFFECT OF INTRAPLANTAR (i.pl.) ADMINISTRATION OF PD 198306 ON STREPTOZOCIN-INDUCED STATIC ALLODYNIA



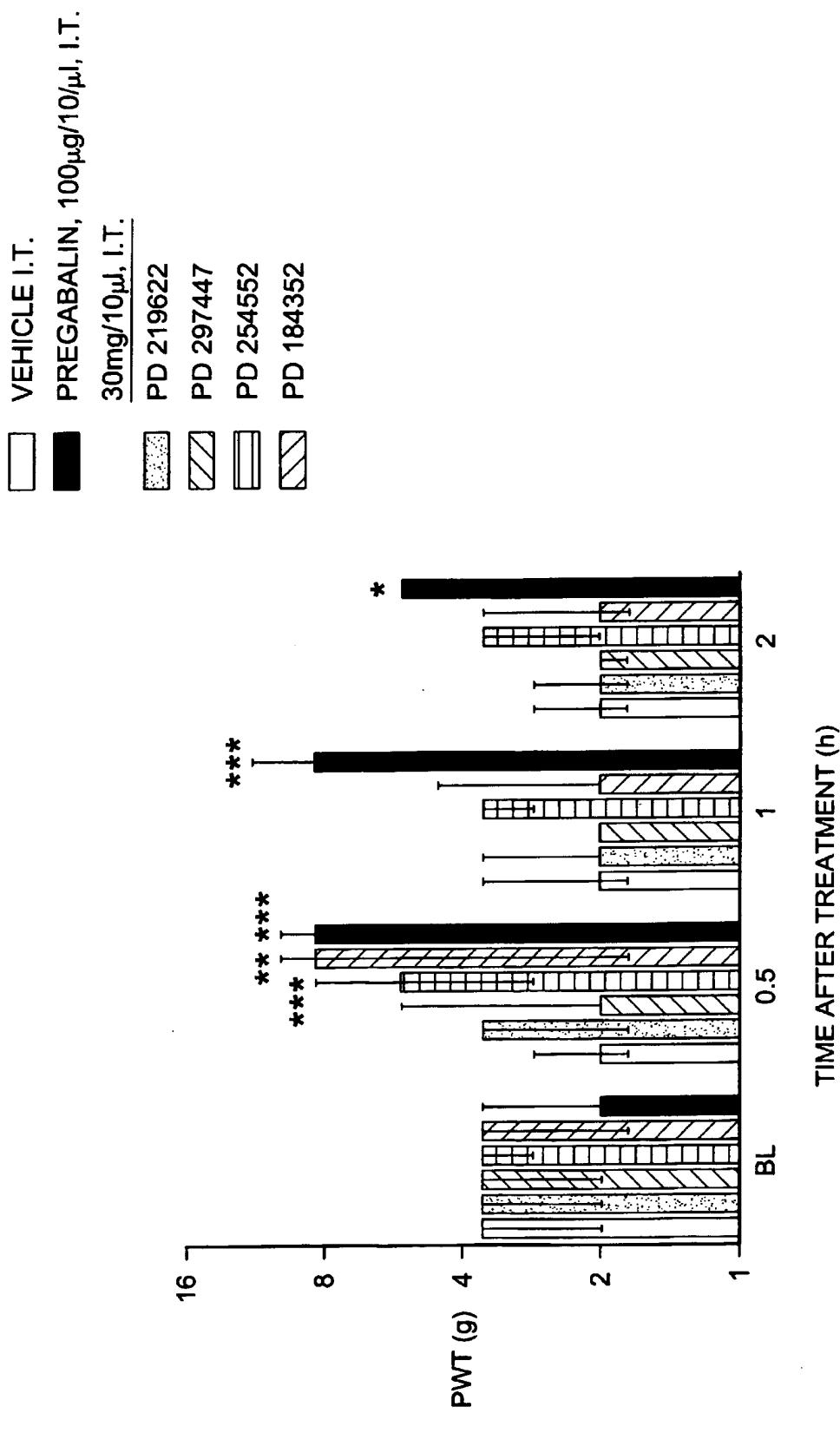
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FIG. 7  
EFFECT OF INTRAPLANTAR (i.p.) ADMINISTRATION OF PD 198306 ON  
CCI-INDUCED STATIC ALLODYNIA



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**FIG. 8**  
**EFFECT OF INTRATHECAL (i.t.) ADMINISTRATION OF PD 219622, PD 297447, PD 184352,  
 PD 254552 OR PREGABALIN ON CCI-INDUCED STATIC ALLODYNIA**



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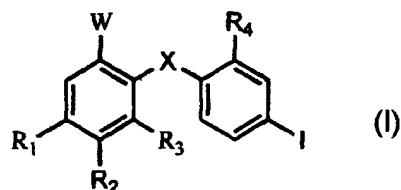
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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WO 01/05391 A3

(54) Title: METHOD FOR TREATING CHRONIC PAIN USING MEK INHIBITORS



(57) Abstract: The invention features a method for treating chronic pain using the diarylamines disclosed in formula (I) of claim 1.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/18346

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 A61K31/41 A61K31/4245 A61K31/42 A61K31/433 A61K31/4196  
A61K31/425 A61P25/04

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.       |
|-----------|--|-----------------------------|
| E         | WO 00 42029 A (BARRETT STEPHEN DOUGLAS ;BRIDGES ALEXANDER JAMES (US); WARNER LAMB) 20 July 2000 (2000-07-20)<br>cited in the application<br>page 4, line 29,30; claim 34<br>---- | 1,7,8,<br>11-33             |
| P, X      | WO 00 35436 A (DUDLEY DAVID THOMAS ;FLORY CRAIG MASON (US); SALTIEL ALAN ROBERT ()<br>22 June 2000 (2000-06-22)<br>page 1-2; claim 7; example 208<br>page 83, line 29<br>----    | 1,4,7,8,<br>10,12,<br>13,20 |
| Y         | WO 98 37881 A (BRIDGES ALEXANDER JAMES ;WARNER LAMBERT CO (US))<br>3 September 1998 (1998-09-03)<br>page 83, line 28; claim 7; example 208<br>----                               | 1-33<br>-/-                 |

Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

12 January 2001

Date of mailing of the international search report

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## INTERNATIONAL SEARCH REPORT

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|----------|--|-----------------------|
| Y        | WO 99 01421 A (DOHERTY ANNETTE MARIAN ; BARRETT STEPHEN DOUGLAS (US); BRIDGES ALEX) 14 January 1999 (1999-01-14)<br>page 5, line 1-15<br>claims; example 208<br>---  | 1-33                  |
| P, Y     | JI RU-RONG ET AL: "Nociceptive-specific activation of ERK in spinal neurons contributes to pain hypersensitivity." NATURE NEUROSCIENCE, vol. 2, no. 12, December 1999 (1999-12), pages 1114-1119, XP000978586<br>ISSN: 1097-6256<br>page 1117, column 2; claim 5<br>---                                    | 1-33                  |
| A        | DUNCIA J V ET AL: "MEK inhibitors: the chemistry and biological activity of U0126, its analogs, and cyclization products" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 8, no. 20, 20 October 1998 (1998-10-20), pages 2839-2844, XP004139571<br>ISSN: 0960-894X<br>the whole document<br>--- | 1-33                  |
| A        | BEKEMEIER H ET AL: "STRUCTURE-ACTIVITY RELATIONSHIP IN NONSTEROIDAL ANTIINFLAMMATORY AGENTS, INCLUDING OSAR IN FENAMATE DERIVATIVES" AGENTS AND ACTIONS SUPPLEMENTS, CH, BIRKHAUSER VERLAG, BASEL, 1 July 1982 (1982-07-01), pages 17-34, XP002063635<br>ISSN: 0379-0363<br>the whole document<br>---      | 1-33                  |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/18346

| Patent document cited in search report | Publication date | Patent family member(s) |  | Publication date |
|--|------------------|-------------------------|--|------------------|
| WO 0042029                             | A 20-07-2000     | AU 2482700 A            |  | 01-08-2000       |
|  |                  | JP 2000204077 A         |  | 25-07-2000       |
| WO 0035436                             | A 22-06-2000     | AU 2185800 A            |  | 03-07-2000       |
| WO 9837881                             | A 03-09-1998     | AU 5610398 A            |  | 18-09-1998       |
|  |                  | ZA 9801578 A            |  | 02-09-1998       |
| WO 9901421                             | A 14-01-1999     | AU 8262698 A            |  | 25-01-1999       |
|  |                  | BR 9810385 A            |  | 05-09-2000       |
|  |                  | EP 0993437 A            |  | 19-04-2000       |
|  |                  | HR 980369 A             |  | 30-04-1999       |
|  |                  | ZA 9805726 A            |  | 27-01-1999       |

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